Corticospinal Facilitation during Hand Laterality Judgments?

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Contribution

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Summary

Observing others performing actions is a common way to learn new motor skills. Such ability appears to be linked with one's ability to imagine actions (motor imagery) (Wang et al. 2014). While motor imagery has been widely used in the context of athletic performance, the same approach has also been advocated in rehabilitation settings, where they often target populations with chronic pain using mobile health applications **(**de la Vega and Miro 2014**)**. However, we still have very limited information as to how the ability to perform motor imagery addresses this rehabilitation application **(**Johnson et al. 2012**)**. In the present study, we examined this question by looking at modulation in corticospinal excitability in the context of a motor imagery task. The imagery task itself consisted of judging whether images depicting hands in different postures represented either right or left hands. Based on prior neuroimaging and chronometric studies, such laterality judgments about hand postures are thought to involve mental rotations of one's own hand (i.e., a form of implicit motor imagery) and thus provided an ideal context to evaluate if advocating such strategy is a valid approach to elicit motor activation in rehabilitation patients (Butson et al. 2014; Goble and Brown 2008; Parsons 1987**)**. To this end, we used non-invasive transcranial magnetic stimulation (TMS) to probe the excitability of the motor system while young healthy participants performed mental rotations in the hand judgment task. Corticospinal excitability was tested in both hemispheres separately (target muscle: first dorsal interosseous) with participants (n=18) seated in front of a computer screen while they performed hand laterality judgments using a commercial set of pictures depicting bare hands in different postures. Excitability was tested also under two other conditions to contrast with variations measured during the hand laterality task, i.e. a mental counting task and a control task (looking at the image of a static foot). In all conditions, TMS (110% resting motor threshold) was set to trigger at ~half of the mean response time in the hand laterality task measured prior to testing with TMS. Comparison of task-related variations in MEP amplitude revealed no significant hemispheric main effect or interaction, although MEPs tended to be larger in general in response to left TMS. A “task condition” effect was observed owing to the large MEP facilitation elicited during the mental counting task, which was significantly different ($p<0.001$) from either the control “Foot” task or the hand rotation task. In fact, the latter task tended to be associated with MEP depression. A secondary experiment involving a subset of participants ($n=6$) to examine the influence of image contents (i.e. hand performing actions instead of bare hands) and probing more proximal muscles produced similar results as the main experiment. These results indicate that the general assumption that laterality tasks involving body parts will lead to internal mental rotation and motor activation and enhanced excitability is not necessarily true. In fact, our observations suggest that participants may rely on non-motor strategies based on visual cues when making laterality judgments about body parts. As well, no evidence for hemispheric asymmetry was found with the hand laterality task which is in line with other recent reports. Collectively, these results highlight the need to exert caution when using laterality tasks for rehabilitation purposes. One cannot simply assume that such tasks will translate into motor simulation and facilitation of the motor system. More research should be undertaken before recommending the hand mental rotation task as a viable rehabilitation option for chronic pain.

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General introduction

The control of human motor imagery (MI) is purported to be made possible by the intricate system of mirror neurons and their associated areas within the nervous system (Rizzolatti and Craighero 2004). This motor imagery network is spread out across many different brain regions and helps humans understand and learn specific movements (Hanakawa et al. 2008). The ability to engage the mirror neuron network to effectively create motor imagery is well supported in the literature for young healthy people. This ability is being targeted at the level of sensorimotor processing in order to treat chronic pain using mobile health applications, such as the NOI Recognise™ application (Wajon 2014). However, it is not yet clear whether this ability is beneficial in chronic pain populations.

While there has been some controversy regarding the specific lateralization of motor imagery within the brain, it is becoming more apparent that this task is more rightly lateralized overall (Munzert et al. 2009). Many factors play into this lateralization, including stimulus type (Tomasino and Rumiati 2004) and strategy (Lebon et al. 2012). Alternately, language processing has traditionally been localized within the left hemisphere (Bookheimer 2002) owing to the presence of dedicated temporo-frontal circuits to process language understanding in Wernicke’s area and speech production (Broca’s area) (Hinke et al. 1993). With this in mind, it is possible to analyze potential differences between motor imagery tasks and internal vocalization tasks.

In the next chapter, I will review the recent literature regarding mirror neuron networks involved in action representation, corticospinal facilitation during action representation, and the effect of laterality on motor imagery. By examining these issues, I will also briefly tackle some of the controversies surrounding the use of motor imagery as a strategy to relieve chronic pain.

Chapter I: Literature review

1. Parieto-frontal cortical networks involved in action representation

Humans display a very keen ability to learn by observing their conspecifics. Indeed, through observation one can easily detect specific kinematics and kinetics cues to allow efficient movement reproduction, which provides the basis for action imitation (Sakadjian et al. 2014). At another level, action observation can also lead to understanding of meanings and intentions associated with gestures, which reflects higher order processing in the brain (Jeannerod 2001). In the last two decades, our understanding of the neural processes underlying such ability to learn by observation has progressed substantially in parallel with the development of neuroimaging techniques. It now seems clear that action observation and motor imagery both represent covert stages of motor execution, where actions are planned but not overtly executed (Jeannerod 2001). As proposed by Jeannerod (2001), observing and imagining actions are functionally equivalent processes relying on internal motor simulation and, as such, are mentally executed actions that remain, however, at the planning level.

In this section, I will discuss the mirror neuron network as it relates to motor imagery and action observation. Further, the dispersion of the mirror neuron network among the different regions of the brain will be explored.

1.1. Functional role of the mirror neuron network

The parieto-frontal network along with the superior temporal sulcus, are thought to be at the basis of the mirror neuron system (MNS) in humans (Gallese et al. 1996; Iacoboni et al. 2001; Rizzolatti et al. 2001). The MNS is proposed to be utilized by humans to learn and understand movement (Rizzolatti et al. 1996). It does so by either mirroring the actions of others or by eliciting a mental rehearsal of movement (Dushanova and Donoghue 2010). Mirror neurons are interspersed with other neurons which are responsible for action and fire both when viewing or performing an action (Dushanova and Donoghue 2010). They are found primarily in the premotor cortex, supplementary motor area, primary somatosensory cortex, and the inferior parietal cortex (Molenberghs et al. 2009) and have been proposed as a possible mechanism for action knowledge acquisition (Collins 2007). The mirror neuron system does not respond to biomechanically impossible movements. For example, Costantini et al. (2005) using fMRI found that participants exhibited activation of the mirror neuron system while observing actions defined as biomechanically possible whereas they showed none while viewing actions deemed biomechanically impossible. Rather, the MNS responds only to natural actions and thus has been linked to the recognition and understanding of actions (Rizzolatti et al. 2001). It is proposed that mirror neurons mimic a specific firing pattern during observation of movement which can then later be used to recreate that same movement (Rizzolatti et al. 1988). In support of this contribution to motor learning, numerous studies have found activation of the MNS (primarily the superior parietal lobule) when participants have been asked to observe movement to imitate but not when they were simply asked to observe that same movement with no intention to imitate (Buccino et al. 2001; Grezes 1998; Iacoboni et al. 1999). In sum, mirror neurons are said to act by recognizing firing patterns associated with viewed movements and contribute to motor learning.

1.2. Frontal Lobe: inferior frontal gyrus and premotor areas

The inferior frontal gyrus (IFG) is a region of the frontal lobe which has traditionally been associated with the inhibition of motor action (Aron et al. 2004). In recent years, the IFG

(Brodmann’s areas 44 & 45) has been attributed an inhibitory role within the primate mirror neuron system (Decety 1996; Munzert et al. 2008). Notably, the IFG has a role equivalent to the ventral premotor areas (PMv) in non-human primates and was also the first region where mirror neurons were described in primates (Rizzolatti and Craighero 2004). The PMv is a critical node in the mirror neuron system and is thought to serve to cluster together observed actions that are performed with the final effectors (Pelphrey et al. 2005; Sakreida et al. 2005; Wheaton et al. 2004). Mirror neurons found in distinct clusters within the IFG have been consistently activated while human volunteers observed or imitated actions performed by others in various studies (Grafton et al. 2001; Hari et al. 1998; Iacoboni et al. 1999). It is hypothesized that mirror neurons, and by extension the IFG, play an important role in the learning and understanding of movements and as such make up part of the specialized fronto-parietal circuit together with the supramarginal gyrus (Rizzolatti and Sinigaglia 2010). The IFG is thought to match observed actions with existing internal representations while attempting to internalize their compatriot’s goals or intentions (Rizzolatti and Sinigaglia 2010). Interestingly, activation in the IFG via the mirror mechanism has been shown to increase with age, as a compensatory mechanism for learning (Ward 2006). In sum, the IFG paired with the supramarginal gyrus creates a specialized fronto-parietal circuit which enables mirror neurons to infer intentions or goals via observed behavior in order to understand and learn motor actions.

1.3. Parietal lobe: inferior and superior parietal lobule

The inferior and superior parietal lobules of the parietal lobe are thought to contribute to planning and the online control of motor imagery and movement actions. They both have specialized interconnected functions which contribute to this. Firstly, the inferior parietal lobule, or IPL, is activated during mental rotation and is thought to be involved in the monitoring of limb positioning, whether the movement be imaged or executed. Patients with lesions of the IPL exhibit deficits in achieving target postures during movement (Goldenberg 2001) without affecting other movement parameters such as speed of execution (Sunderland and Sluman 2000). Based on these observations, it has been argued that the IPL might play a distinct role in comparing intended and actual postures (Vargas et al. 2004). Further to this, it has been found that this ability to compare postures is dependent upon which perspective the individual is undertaking motor imagery. In a study by Ruby & Decety (2001), first- and third-person imagery was compared in healthy participants. Their findings indicated that first-person imagery predominantly involved the left IPL while third-person imagery primarily used the right IPL (Ruby and Decety 2001). It was concluded that the left IPL is preferentially activated when planning one's movements whereas the right IPL is more active in interpreting others' behavior which was supported by the findings of both Decety et al. (1997) and Grezes (1998).

Likewise, in addition to activation during motor imagery, the left IPL has also been found to be active during action observation which suggests that the parietal lobules are intricately linked with the temporal lobe. Specifically, when subjects viewed stationary hands but were not told they would be imitating their positions, activation of the left IPL occurred (Grezes 1998). In support of these results, Positron Emission Tomography (PET) studies also found activation of the IPL during action observation (Grafton et al. 1996; Rizzolatti et al. 1996). Of note, all the above selected findings relate only to movements of the hands which suggests that the IPL is heavily involved in hand imagery and gestures (Grezes and Decety 2001). The activity of the left IPL during both observation with no intent to act and during 1st person motor imagery is puzzling and creates a need for further investigation with a technique like TMS that may uncover more specific variation within the MEPs.

Concerning the superior parietal lobule (SPL), much like the IPL it similarly codes for the posture position of the contralateral limb. In essence, the SPL integrates visual and somatosensory inputs regarding the relative position of contralateral limb with respect to the body (Wolbers et al. 2003). The information gathered from the inputs is then relayed to premotor areas to plan for reaching actions (Wolbers et al. 2003). As a result of the coding for limb position, the SPL appears to help to properly adjust posture during imagined movement (Crammond 1997). Support for this hypothesis comes from a study involving a participant with a lesion localized to the SPL (Wolpert et al. 1998). The participant, PJ, had weights placed on the hand contralateral to her lesion out of her line of view. After a period of delay while her hand and arm were motionless, she was asked if there was a weight on her hand or not. She was no longer able to detect the weight on her hand, but was able to perceive when the weight was removed afterwards due to the associated minor movement. It was concluded that PJ had difficulty in maintaining an internal representation of the body’s static positional state due to her SPL lesion (Wolpert et al. 1998). In addition to its role in coding limb position, the SPL appears to also be involved in mental rotation of hands. In a PET study, it was found that the SPL was selectively active while mentally rotating images of hands, but not when rotations involved branching objects made up of blocks (Kosslyn et al. 1998). Therefore, the SPL is likely responsible for signalling arm and hand position for the planning of reach and grasp actions as well as awareness of body positioning. Further, it is likely involved in the mental rotation of hands and seems a critical node in the parieto-frontal network during action representation, either mentally simulated or executed.

1.4. Temporal Lobe: superior temporal gyrus

Localized within the temporal lobe of the human brain, the superior temporal gyrus (STG) is generally associated with the perception of auditory cues, the recognition of emotion in facial expressions and language acquisition (Kosslyn et al. 2001). However, when investigated in terms of motor imagery, observation, and movement execution, its role is still being investigated. Specifically, the role of the STG seems to be limited to observation of movement (Grezes and Decety 2001). The STG is likely involved in distinguishing between human goal-directed movements and non-human random movements (Howard et al. 1996). This was shown by Howard et al. (1996) in an fMRI study using a point-light technique to represent the human action of running as compared to random dot generation. Their results revealed a bilateral activation of the superior temporal gyrus, among other activation. In another experiment, STG activation was detected while observers watched goal-directed body movements (Schultz et al. 2004). Lastly, the corresponding superior temporal polysensory area (STPa) in primates contains neurons which are also responsive to the observation of body movements which lends support to the argument that the STG in humans may be responsible for human movement recognition (Oram and Perrett 1994). Taken together, these findings suggest that the STG may be responsible for positively identifying human goal-directed movement during action observation.

2. Corticospinal facilitation during action observation, imagery and action execution

2.1. Transcranial magnetic stimulation: Explanation of technique

Transcranial magnetic stimulation (TMS) is a non-invasive technique that was developed in 1985 to stimulate the human brain to probe corticospinal excitability (Barker et al. 1985). TMS works by passing a high voltage changing current (3 kV) through a coil to create a brief intense magnetic field (1-2 Tesla). This magnetic field in turn will pass through the skin and skull to induce an electrical current (~100 µs duration) in the underlying neural tissues that will result in depolarization of cortical neurons (Terao and Ugawa 2002). This technique has significantly advanced the neurophysiological investigation of the motor cortex (Rossi et al. 2009). In the context of this study, TMS will be used to assess task-dependent variations in corticospinal excitability from the monitoring of changes in motor evoked potential (MEP) amplitude. The MEP amplitude can be described as the electromyographic (EMG) response measured from peak-to-peak following a single pulse of TMS at a given intensity relative to the person's resting motor threshold (RMT) (Talelli et al. 2006). The amplitude provides a direct measure of the intrinsic as well as the extrinsic excitability of cortical and spinal motoneurons (Taube et al. 2006).

2.2. Corticospinal facilitation during action execution

It is widely known that corticospinal excitability is facilitated during movement execution (Wassermann 2002). This facilitation manifests itself in the form of increased MEP amplitudes (Wassermann 2002). The mechanism for this facilitation is proposed to be that voluntary activation increases the number and size of descending volleys and also lowers the firing threshold of spinal motoneurons via incoming peripheral afferents (Di Lazzaro et al. 1998; Mills and Kimiskidis 1996; Ugawa et al. 1995). For example, in a study by Clark, Tremblay & Ste-Marie (2004), MEPs were recorded from the first dorsal interosseous of the dominant hand in five conditions: passive observation, observation to imitate, imagery, imitation, or counting backwards mentally. For the observation conditions, participants watched five second video sequences of hand actions performed by a model. Not surprisingly, the findings indicated that imitation produced the most facilitation as shown by an increase in MEP amplitude relative to baseline measures.

More specifically, it is important to note that corticospinal facilitation during action execution can be task-specific. As shown in a prior study involving a tactile discrimination task, subjects exhibited greater facilitation when engaged in a task that required them to discriminate a raised 2-dimensional surface versus a task that required them to discriminate between surface roughness (Master and Tremblay 2010a). In another study from the same group, it was determined that intra-active haptic touch (touching oneself) induced more corticospinal facilitation than interactive (touching another person) haptic touch (Master and Tremblay 2010b). These are but two examples of task-dependent corticospinal excitability modulation studies which have focused solely on fine motor skills. When fine motor skills are compared to gross motor skills, it has been shown that fine motor skills induce more corticospinal excitability due to the increased cognitive demands of the tasks (Datta et al. 1989; Schieppati et al. 1996). The issue can also be looked at in terms of task complexity. It appears that more complex tasks, such as tasks which require sequential movements, require more cognitive demand and thus create greater corticospinal facilitation (Flament et al. 1993). In sum, corticospinal facilitation during action execution can be affected by a number of factors, including the degree of attention and complexity dictated by task conditions.

2.3. Corticospinal facilitation during action observation

Corticospinal excitability can be facilitated while humans observe actions (Loporto et al. 2011). However, not all observed actions produce facilitation. Specifically, observation of natural human actions will produce more robust and consistent facilitation when compared to abstract (non-human) actions or biomechanically impossible actions (Fadiga et al. 1995a). For example, Fadiga et al. (1995a) showed that participants who observed the experimenter manipulating common objects with their hands exhibited more robust and consistent facilitation than when they just observed those same objects attentively for a similar period of time. The facilitation produced by action observation is similar in magnitude to that elicited with motor imagery (Clark et al. 2004). Furthermore, the patterns of MEP changes in task specific muscles elicited by TMS during action observation closely resemble those seen during action execution (Fadiga et al. 1995b). These patterns of activation due to observation act on the same muscles that would be used to perform the observed action (Strafella and Paus 2000). Interestingly, intention to act on observations has been shown to have no effect on the amount of facilitation elicited (Kiers et al. 1993). The motor system is not solely devoted to the production of movements but is also geared towards the recognition of movements (Fadiga et al. 1995a).

2.4. Corticospinal facilitation during motor imagery

Corticospinal facilitation has been consistently shown in motor imagery tasks involving healthy young adults (Kasai et al. 1997; Oku et al. 2011). Although motor imagery produces similar activation in some overlapping areas compared to action execution, the corticospinal excitability is slightly lower (Rossini et al. 1999). It is plausible that this relative reduction of corticospinal excitability between imagery and action execution may be attributed to a certain amount of gating which occurs at the subcortical level to prevent overt movement from occurring (Beisteiner et al. 1995). Further, according to Cunnington et al. (1996), it appears that motor imagery and movement execution share the same pre-movement preparatory phases, mostly involving the supplementary motor area, but motor imagery never surpasses the covert stage which is likely due to inhibitory processes.

One way to explore the differences in corticospinal excitability between action execution and MI is to use a mental rotation task. The mental rotation task can be used to evaluate the ability of individuals to effectively use motor imagery in order to make certain judgments about visual objects (Kosslyn et al. 1998). However, corticospinal excitability varies depending on the different types of objects presented to the participant. For example, the mental rotation of hands has been found to activate the precentral gyrus, the SPL & IPL, primary visual cortex and insula whereas the mental rotation of branching objects induces activation in the parietal lobe only (Kosslyn et al. 1998). In theory, determining the laterality of a visually presented hand involves two separate stages. The first stage rapidly assesses the laterality of the hand and the second confirms the assessment with a mental rotation of the image (Ni Choisdealbha et al. 2011). While the mental rotation of normal hands produces bilateral activation of premotor areas, interestingly, the mental rotation of hand tools produces unilateral premotor activation which suggests that the brain takes into account the preferred limb for manipulating that tool (Vingerhoets et al. 2002).

To summarize, TMS has been used extensively to assess the contribution of the motor cortical system to action representation, either covertly (action observed or imaged) or overtly executed. TMS investigations in this regard have highlighted the role of subliminal corticospinal facilitation when individuals are engaged in covert execution associated with observation or mental simulation of hand actions.

3. Laterality

Whenever research focuses on hand actions, whether real or imagined, it is important to examine the issue of laterality, as ~90% of the population display preference for the right hand over the left hand. In the next section, I will briefly review issues related to handedness and dominance in the context of motor imagery.

3.1. Hemispheric specialization in relation to handedness and language

An important and understudied individual factor related to motor imagery is hemispheric specialization in relation to handedness. Roughly 90% of the general population exhibits a preference for the right hand which raises the question as to whether this asymmetrical hand use is reflected at the level of sensorimotor organization. In fact, recent studies suggest that the dominant hemisphere (i.e. the left in most people) is specialized for planning limb trajectory, whereas the non-dominant hemisphere (right hemisphere) is rather specialized in specifying final limb position (Bagesteiro and Sainburg 2002; Sainburg 2005). Such organization would tend to favor the left hemisphere in motor imagery tasks, as the planning of trajectory is crucial for movement execution. However, the issue is further complicated by evidence linking the processing of kinesthetic inputs with the right hemisphere, whereas visual information would be mostly processed in the dominant left hemisphere when guiding movements (Goble and Brown 2008). In this latter perspective, it is the right, and not the left, hemisphere that would display greater importance when imagining performing actions (kinesthetic motor imagery). When one considers these different perspectives on the role of hemispheric specialization in motor control, it is not surprising to find inconsistent results in the literature. For instance, TMS studies that have compared hemispheric differences in motor facilitation associated with motor imagery tasks have produced mixed results, some finding asymmetries in support of the left hemisphere dominance (Yahagi and Kasai 1999), while others could not find such asymmetries (Aziz-Zadeh et al. 2004). The issue of hemispheric specialization thus remains highly controversial.

Looking a little closer, it is possible to shed a little light to help explain the controversy surrounding the lateralization debate. One way to tackle the controversy is by examining patients with unilateral brain damage. For example, Danckert, Ferber, Doherty, Steinmetz, Nicolle, & Goodale (Danckert et al. 2002) used the speed-accuracy trade-off to compare actual goal directed movements with imagined goal directed movements in a case study of a patient with a right parietal lesion. The patient was instructed to point to targets of various sizes, either physically or imagined. While they found that the patient's physical movements exhibited the classic signs of the speed-accuracy trade off (slowed execution when pointing to smaller targets), his imagined movements were equally fast no matter the size of the target (Danckert et al. 2002). Interestingly, this phenomenon was exhibited using both hands, and not simply the contralateral left hand (Danckert et al. 2002). These results suggest that the right hemisphere is intricately linked with the generation of internal models (Danckert et al. 2002). In contrast, other studies in patients with unilateral brain damage have found divergent results (Mutsaarts et al. 2006; Steenbergen et al. 2004). To explain these conflicting results, Steenbergen, van Nimwegen, & Crajé (Steenbergen et al. 2007) proposed that perhaps the hemispheric difference could be due to participants' alternative strategies when performing mental rotation of hands. Specifically, their results showed that people may choose to use either a first person (motor imagery) or a third person (visual imagery) strategy (Steenbergen et al. 2007). These findings are in line with those of Lebon, Lotze, Stinear, & Byblow (2012) who made similar observation regarding strategies when comparing implicit motor imagery (hand laterality task) with explicit motor imagery (rotating objects). Practically, this means that people may circumvent the task altogether which could explain a lack of right hemispheric dominance when allegedly completing motor imagery during mental rotation.

Although controversy still exists as to the hemispheric contribution debate, it seems plausible to assume that motor imagery is a process lateralized mainly to the right hemisphere. Evidence for this has been growing over time (Munzert et al. 2009; Stinear et al. 2007). For example, some of the confusion on the issue may derive from the stimulus type as seen previously. Tomasino and Rumiati (2004) found that the lateralization of mental imagery was more left lateralized using Shepard & Metzler stimuli (branching block figures) but was predominantly right lateralized when using human hands. Additionally, Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni in a study of mirror neuron activity found that visuomotor transformations were predominantly right lateralized while the left hemisphere was more involved in language processing (Aziz-Zadeh et al. 2006).

Language processing remains much less controversial than motor imagery in terms of hemispheric specialization. There is ample evidence that contends that it is lateralized to the left hemisphere. Indeed, this has been shown as early as eight years of age (Balsamo et al. 2002). Support for this comes from the fact that Broca’s area (classically linked with language processing) resides in the left hemisphere (Hinke et al. 1993). Further to this, Broca’s area can be further subdivided into regions which react differently based on stimulus type (Newman et al. 2003). The authors used fMRI to show that different types of ungrammatical sentences could yield variability in cerebral blood flow to the different sub regions of Broca’s area (Newman et al. 2003). Lastly, similar left lateralized activation was shown to take place during mental counting tasks using the subtraction of prime numbers (Burbaud et al. 1995).

The differential lateralization of motor imagery and language processing provides an interesting context to attempt to determine whether there are differences between hemispheres in terms of motor facilitation when participants are engaged in mental tasks in the motor or cognitive domains. These questions are critical not only to provide a better understanding of the neural basis of motor imagery but also for practical reasons since motor imagery tasks are currently advocated for the relief of chronic pain in the extremities (Mendez-Rebolledo et al. 2017). For instance, The NOI Recognise™ mobile application is currently available on the market to assist patients with chronic pain to get relief by activating the cortical networks associated with sensorimotor processing (Johnson et al. 2012). It that sense, it seems critical to determine whether mental rotation of body parts leads to differential modulation in the hemispheres, a finding that could potentially influence the way applications are designed for clinical interventions for patients with unilateral limb pain.

4. Neurophysiological basis for motor imagery in rehabilitation of chronic pain

When examining the issue of imagined and executed actions in the context of rehabilitation programs, it is imperative that we attempt to clarify if there is a neurophysiological rationale for their use. For example, a randomized controlled study comparing motor imagery to ongoing conservative treatment (Moseley 2004) lent support to the notion that motor imagery is an effective rehabilitation strategy for regional chronic pain syndrome. The author found that the use of motor imagery significantly reduced the subjects' perceived pain scores as compared to conservative treatment (Moseley 2004). However, as alluded to above and supported by rehabilitation practitioners in clinical settings (Johnson et al. 2012), some doubt remains as to whether or not using motor imagery and specifically the mental rotation task is practical. It stands to reason that the dissociation of the effectiveness of motor imagery between research and clinical settings could be attributed to the involvement of the primary motor cortex. In a case study involving a clinical chronic regional pain syndrome patient, King et al. (2015) uncovered upon debriefing that their patient had been using third person motor imagery rather than first person motor imagery during a foot mental rotation task and in doing so, they were able to perform the task with ease. However, when the patient was asked to specifically imagine themselves performing the rotations, they reported pain and exhibited significantly worse accuracy in their affected limb responses (King et al. 2015). The authors concluded that the patient likely was not engaging in motor activity during third person motor imagery which resulted in pain-free motor imagery and more accurate scores (King et al. 2015). The use of alternative strategies could help explain the lack of consensus among researchers regarding whether or not the primary motor cortex is involved in motor imagery.

Some debate surrounds M1 involvement in mental rotation tasks. For instance, TMS studies have measured response times and accuracy while manipulating pulse timing during mental rotation tasks to find that the left M1 activity is significantly modulated during mental rotation tasks (Ganis et al. 2000; Tomasino et al. 2005). Similarly, another study by one of the same groups that contrasted motor imagery strategies found that the egocentric (first person) mental rotation was localized to the left hemisphere whereas allocentric (third person) mental rotation was predominantly localized to the right hemisphere (Tomasino and Rumiati 2004). Alternately, other studies have found conflicting results instead showing no real differences between hemispheres during mental rotation (Bode et al. 2007; Pelgrims et al. 2011). Given that the scientific community has not reached a consensus on the hemispheric lateralization of the mental rotation process, it is imperative that further research is conducted prior to advocating for it as a rehabilitation strategy.

Objectives of the present work

For this thesis project, our goal was to determine whether there are hemispheric differences in terms of corticomotor facilitation when participants are engaged in mental tasks in the motor or cognitive domain. For the motor domain, we used the hand laterality task in which participants are shown pictures of hands and they must determine whether the image represents either a left or a right hand. As stipulated before, such laterality judgments are assumed to reflect internal motor simulation involving mental rotations of one’s own hand and, therefore, provide an ideal context to examine modulation in cortical excitability in relation to imagery tasks (Thayer and Johnson 2006; Thayer et al. 2001). Modulation elicited during hand laterality judgements was contrasted with that observed during either a cognitive task (i.e., mental counting task) or a control task (i.e., viewing a still body part).

Hypotheses

Based on the literature review, we hypothesised that corticomotor facilitation, as reflected in MEP amplitude, would be greater for the hand mental rotation task than either the mental counting or the control task, owing to recruitment of the sensori-motor network associated with motor imagery. We also surmised that the corticomotor facilitation elicited during hand mental rotations would be greater in the right than in the left hemisphere, owing to previous findings of increased right hemispheric specialization during motor simulation.

Chapter II: Methods

1. Participants

Participants consisted of 18 healthy young adults (23.8 +/- 4.0 years, range 18-34 years, 12 men, 6 women) who were asked to come to the laboratory for one session lasting ~ 2 hours. For the purposes of this study, health was defined as the absence of all neurological disease such as multiple sclerosis or Parkinson’s disease, and musculoskeletal disease or injuries that affected the hand such as severe osteoarthritis or forearm fractures. For magnetic stimulation, participants with cardiac stimulators (pace-makers), those with metal implants in the skull, and pregnant women were excluded. Participants received $20 to cover parking and transportation fees associated with their participation.

Potential participants who showed interest in the study were given an information sheet and consent form. They were asked to read the documents carefully prior to the session. After reading the information sheet and upon verbal agreement about their participation, participants were asked to sign the consent form prior to the testing session. Potential participants were also asked to fill out a TMS eligibility questionnaire to determine if they presented with any contraindications for TMS. Before testing, participants were familiarized with the stimuli and properly trained to do the tasks. The procedures used in this study have been approved by the Bruyère Research Ethics Board.

2. Determination of handedness

Handedness was determined using a questionnaire (modified Edinburgh Handedness Inventory index or mEHI, see Appendix A). A behavioural assessment of manual preference was also performed using the grooved pegboard test but the results of this assessment were not included in the present study. Most participants (16/18) were right handed according to the mEHI and the behavioural assessment of manual preference.

3. Performance in the hand laterality task

Participants were trained and tested for their ability to perform fast and accurate judgments about hand laterality using the online version of the "Right-left discrimination Test" developed by the *Neuro Orthopeadics Institute, (Adelaide City, Au*) (http://www.gradedmotorimagery.com). For testing, participants were seated in front of a computer screen and presented with a series of images depicting hands in different orientations. The task for the participant was to judge the laterality (right or left) by pressing the right or left arrows on the keyboard, as quickly as possible. They were asked to not attempt to physically rotate their own hands in an attempt to help them discriminate laterality. The experimenter also watched the participants to ensure compliance with this request. Additionally, participants were also asked to not favour speed over accuracy or vice-versa. This was to ensure that participants did not simply guess the laterality of the hands. Lastly, participants were instructed to not look at their hands. Instead, the experimenter ensured that their focus remained solely on the computer screen. Two blocks of 20 images were presented consecutively, each image having been presented for up to 6 s (the next image was presented immediately after the previous selection). If a response was not recorded within that 6s window, the next image was presented and an error was recorded for the relevant image. Once the test was completed, the performance (accuracy and response time) was displayed on screen and was recorded and saved for later analysis. The accuracy scores were simply used to ensure compliance with the instructions not to guess the laterality of the hands. The response times were used to calculate a mean response time which was subsequently used to adjust stimulus delivery time during TMS (see below). Note that no personal information was stored along with the performance results on the website.

4. Transcranial magnetic stimulation data acquisition

For TMS assessment, participants were seated comfortably in a recording chair with their heads supported by a U-shaped neck cushion to minimize head movements and prevent neck fatigue. TMS was delivered with a Magstim 200 stimulator (Magstim Corp., Dyfed U.K.) connected to a focal figure-of-8 coil (70 mm loop). Motor evoked responses (MEPs) were recorded using electromyographic (EMG) surface electrodes (Ag/AgCl, Kendall Medi-Trace™ 130) placed over the first dorsal interroseous muscle (FDI) of each hand. Prior to EMG placement, the FDI was located and palpated by flexing the thumb against index finger. The area superficial to the FDI was cleaned thoroughly with an alcohol swab and allowed to air dry. Only then was the surface electrode placed on the area. Corresponding electromyographic (EMG) signals were amplified and filtered with time constant 10 ms and a low-pass filter of 1 kHz (AB-621G Bioelectric amplifier, Nihon-Kohden Corp. CA 92610). Signals were subsequently digitized at 2 kHz (BNC-2090, National Instrument Corp.) and relayed to Stimo (custom laboratory software) which controlled stimulus delivery and MEP acquisition. Participants were fitted with a Waveguard^{TM} TMS compatible cap (ANT North America Inc, WI 53719) in order to locate the optimal site ("hotspot") to obtain motor evoked potentials (MEP) in the first dorsal interosseous (FDI) muscle. This hotspot was determined with the coil held at ~45° in the mid-sagittal plane until reliable MEPs could be evoked in the target muscle. This site was marked with a sticker to ensure consistent coil positioning. After determination of the stimulation hotspot, the coil was held in place manually by one of the experimenters to derive specific measures of corticospinal excitability. The experimenter frequently reassessed the coil position to ensure that it remained over the optimal stimulation site throughout the experiment. All TMS testing sessions took place between 9am and 4pm to avoid any diurnal variations in corticospinal excitability (Doeltgen and Ridding 2010).

In each participant, the resting motor threshold (RMT) was determined using the TMS Motor Threshold Assessment Tool (MTAT 2.0) which is a software tool developed to allow for fast estimation of motor thresholds through the maximum-likelihood strategy using Parameter Estimation by Sequential Testing approach. It does so by quickly estimating the minimal intensity required to evoke reliable MEP's in the target muscle in 50% of the trials (Awiszus 2003). This technique involves a pre-set stimulation pattern using the assumption that there will be a response failure (no MEP) for a subthreshold and a successful MEP for a suprathreshold stimulus intensity. The RMT is estimated with 95% certainty following 14 to 17 stimulation (Awiszus 2011). After determination of RMT, a series of MEPs (n=15, intensity, 110% RMT) were recorded at rest in both hemispheres to provide a baseline for corticomotor excitability. The order of initial hemispheric stimulation alternated between each subsequent participant (i.e. participant 1 started with the left hemisphere, participant 2 started with the right hemisphere and so on and so forth). Then, task-dependent changes in MEPs were tested in the context of video presentations. Participants were seated in front of a computer screen (~1 m distance) and different video sequences were presented in a predetermined random order. Each trial began by displaying on-screen instructions to: 1) judge if the image was a right or left hand ("Mental Rotation task" or MRT – which involved the same hand laterality task as above), 2) to simply observe a static image depicting a foot, or 3) to count backwards in their head from a certain number. These instructions were displayed for 2.25 s, and then the images of a hand (hand-laterality task) or a foot (observation-control) were displayed on the computer for 3.75 s. The foot in the observation task was used as a control in order to ensure that any potential activation in the MRT was not attributed to simply observing a human appendage. In the case of the counting task, a single title screen showed a specific number to start with. The verbal report at the end of the counting task provided a control for the verbal report at the end of the mental rotation task. In each trial, a single TMS pulse was delivered at a predetermined personalized time during the task presentation after the instructional screen over the hemisphere contralateral to the tested hand. At 3s, the trial ended and participants were asked to report the laterality of the hand in the case of hand rotations trials. Their response (and correctness) was marked on a datasheet. Overall, 48 trials (i.e., 4 videos “right hand”, “left hand”, “foot” and “count” X 12) were performed on each hemisphere. Intertrial delay was at least 10 seconds and EMG silence was ensured before each stimulation.

5. Data analysis

Results from the Hand Laterality Task in NOI Recognise^{TM} were obtained directly for each participant from the app itself. MEP amplitude (peak-to-peak) data for each trial in each task condition were analyzed using a script developed with MATLAB® to determine mean values for all participants individually. The task-related variations in MEP amplitude were first examined in each task condition relative to baseline to get MEP ratio (i.e. MEP_{task}/MEP_{BL} x 100). This provided a general index to compare levels of task-related changes in corticospinal excitability in relation to baseline resting excitability. For the statistical analyses, only the absolute variations in MEP amplitude by task condition were considered. We then ensured the normality of the distribution using D’Agostino and Pearson tests. Individual MEP amplitudes (µV) were then inputted into a 2 x 4 repeated measures analysis of variance (ANOVA) with “Hemisphere” (left vs. right) as the within-participants factor and “Condition” (4 levels: Silent Counting, Foot Observation, Right Hand Judgments, and Left Hand Judgments) as between-participant factors. Post-hoc tests were performed using Sidak's multiple comparisons test. All comparisons and graphics were made using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, California, USA, http://www.graphpad.com). The significance level was set at $p<0.05$ for all differences and interactions.

Chapter III: Research article

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(Lack of) Corticospinal facilitation in association with hand laterality judgments

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Abstract

In recent years, mental practice strategies have drawn much interest in the field of rehabilitation. One form of mental practice particularly advocated involves judging the laterality of images depicting body parts. Such laterality judgments are thought to rely on implicit motor imagery via mental rotation of one own's limb. In this study, we sought to further characterize the involvement of the primary motor cortex (M1) in hand laterality judgments (HLJ) as performed in the context of an application designed for rehabilitation. To this end, we measured variations in corticospinal excitability in both hemispheres with motor evoked potentials (MEPs) while participants (n=18, young adults) performed either HLJ or a mental counting task. A third condition (foot observation) provided additional control. We hypothesized that HLJ would lead to a selective MEP facilitation when compared to the other tasks and that this facilitation would be greater on the right than the left hemisphere. Contrary to our predictions, we found no evidence of task effects and hemispheric effects for the HLJ task. Significant task-related MEP facilitation was detected only for the mental counting task. A secondary experiment performed in a subset of participants (n=6) to further test modulation during HLJ yielded the same results. We interpret the lack of facilitation with HLJ in the light of evidence that participants may rely on alternative strategies when asked to judge laterality when viewing depictions of body parts. The use of visual strategies notably would reduce the need to engage in mental rotation, thus reducing M1 involvement. These results have implications for applications of laterality tasks in the context of the rehabilitation program.

Introduction

In recent years, mental practice strategies, whereby actions are mentally rehearsed without being overtly executed, have drawn much interest in the field of rehabilitation (Malouin et al. 2013). Such strategies are particularly compelling in patient populations where movement is either impossible (e.g. after paralysis) or severely impaired (e.g., intractable pain). The rationale for using mental practice, as a surrogate method for physical practice, has been based largely on the evidence that imagined actions share to a large extent the same neural pathways as those really executed (reviewed in Hetu et al. 2013). Hence, the interest in implementing mental strategies to maintain or restore sensorimotor representations in patient populations. One form of mental practice strategy that has been particularly advocated in the context of rehabilitation involves the presentation of images depicting body parts (e.g., hand or foot) in different postures to judge on their laterality, i.e., whether they are right or left (Lotze and Moseley 2015). The popularity of laterality tasks is such that a commercially available application (Recognise™ app, http://www.noigroup.com/en/product/btrapp) has been specifically developed for rehabilitation purposes to use on smartphones, tablets or computers. Through laterality judgments, patients are expected to engage in motor simulation by mentally rotating their own limb to align with the depicted limb, thereby activating the relevant sensorimotor representation (Lotze and Moseley 2007). While there is evidence that laterality tasks are beneficial in the management of patients with chronic pain (Moseley 2006), there are still controversies surroundings the neural processes underlying laterality judgments. For instance, the assumption that judgments are always the result of a mental rotation process cannot be generalized given reports that patients might actually use alternative strategies (e.g. visual cues) to decide on the laterality (Vannuscorps et al. 2012; King et al. 2015). In this regard, it is important to recall that reference to implicit motor imagery and mental rotation in the context of laterality tasks was initially inferred from chronometric studies, showing that systematic variations in reaction times when making laterality judgments on hand stimuli presented in different orientations were congruent with the time it actually took to physically align one's limb into the orientation depicted in the image (Sekiyama 1982; Parsons 1987). Further support for the role of motor processes in laterality judgments came from neuroimaging studies revealing recruitment of frontal and parietal areas involved in motor planning when judging hand laterality; including supplementary motor area, premotor cortex and superior parietal lobule (Parsons and Fox 1998; Vingerhoets et al. 2002; Creem-Regehr et al. 2007).

Considering the evidence pointing to a critical role of motor areas in mediating mental rotations of body parts, one would expect neurophysiological studies to show a clear involvement of the primary motor cortex (M1) and its projections in laterality tasks similar to that observed with explicit motor imagery tasks (Grospretre et al. 2016). However, transcranial magnetic stimulation (TMS) studies investigating this issue have produced a rather inconsistent picture. For instance, different groups have tested the role of M1 in mental rotations by examining changes in response time and accuracy in response to TMS pulses delivered at various time points during hand laterality judgments. Using this interference approach and comparing the impact of left and right hemispheric stimulation, early investigations concluded that the left M1 had a causal role in mental rotation of hands associated with laterality judgments (Ganis et al. 2000; Tomasino et al. 2005). A subsequent investigation by Sauner et al. (2006) reached an opposite conclusion, however, their results showing no effects of TMS pulses over a wide range of intervals (from 200 to 1000 ms) post-stimuli presentation during laterality judgments. Interestingly, these authors also reported a differential modulation of corticospinal excitability, as reflected in motor evoked potentials (MEPs), which were depressed on the left hemisphere when judging left hands, but facilitated on the right hemispheres when judging right hands. The fact that these changes were detected at a very early stage after stimuli presentation indicated that they were unlikely involved in the mental rotation process. Bode et al. (2007) came to a similar conclusion with regards to the role of M1 in mental rotations and associated modulation in corticospinal excitability, their results showing nonspecific modulation during either implicit (hand laterality) or explicit visual imagery (imaging objects) tasks. More recently, Pelgrims and colleagues (Pelgrims et al. 2009; Pelgrims et al. 2011) using sub-threshold repetitive TMS applied to either the left M1 or right M1, reported a significant increase in response time when judging laterality of hand drawings, whereas such stimulation had no effect on performance in control tasks (letter rotation task and finger naming task). For these authors, this dissociation demonstrated unequivocally the causal role of the M1 in mental rotations underlying laterality judgments.

In the present study, we sought to characterize further the involvement of M1 and its projections in mediating mental rotations in the context of laterality judgments. In particular, we were interested in examining modulation of excitability when laterality judgments are performed in a context similar to that proposed to patients through a training app. Based on the reviewed evidence, we hypothesized that laterality judgments would lead to a selective increase in corticospinal excitability when compared to another mental task linked with numerical processing (mental counting task) or a control task (simple viewing a body part). We also hypothesized that facilitation associated with laterality judgments would be greater on the right M1 than the left M1, given evidence of a predominant role of the right hemisphere in the processing of kinesthetic information (Naito et al. 2005), especially with regards to hand movements (Hagura et al. 2009).

Materials and Methods

Ethics Statement

The procedures described herein were approved by the Research Ethics Board at Bruyère Research Institute in Ottawa, Ontario, Canada. All participants provided written informed consent in accordance with the Declaration of Helsinki. All trials were performed in a controlled laboratory environment. Every participant received a small honorarium for their participation.

Participants

Eighteen young healthy participants (23.8 ± 4.0 years, range 18-34 years, 12 men, 6 women) were recruited from the community in the Ottawa-Gatineau area. The majority of participants were right handed (16/18), as determined by the Edinburg Handedness Inventory (Oldfield 1971). All participants were screened for contraindications to TMS before participation using a health questionnaire (Adapted from Keel et al. 2001).

Hand Laterality Task (HLT)

Participants were trained to perform the HLT using the NOI Recognise^{TM} application (www.noigroup.com/recognise). The Recognise^{TM} app was designed for rehabilitation purposes and allows for measurement of the ability to recognize left and right body parts. For testing, participants were seated comfortably in front of a portable computer (37.5 cm screen) running an on-line version the Recognise^{TM} app. After a period of familiarization, participants were presented with a selection of 40 images of left and right hands (20 images per hand) to discriminate. The images consisted of bare hands in different postures and were presented for 6 s in a random order. In each trial, participants were asked to report as quickly as possible whether the image corresponded to either a right or a left hand by pressing the corresponding keys (← or →) on the computer. Participants were instructed to stay immobile during trials and refrain from engaging in active movements to ensure that no physical strategy interfered with the laterality judgments. The performance was recorded both in terms of accuracy (% correct) and in terms of mean recognition time (MRT). The latter measure (i.e., MRT) was subsequently used to adjust stimulus delivery time to test excitability during the TMS experiment (see below).

Transcranial Magnetic Stimulation

TMS was performed with participants comfortably seated in a recording chair using a Magstim 200 stimulator (Magstim Co. Whitland, UK) connected to a figure-of-eight coil (P/N 3190, Magstim Co.). Motor Evoked potentials (MEPs) were recorded using auto-adhesive electrodes (Ag/AgCl, Kendall Medi-Trace^{TM} 130) placed over the first dorsal interosseous (FDI) of each hand. Electromyographic (EMG) signals were amplified and filtered with a time constant 10 ms and a low-pass filter of 1 kHz (AB-621G Bioelectric amplifier, Nihon-Kohden Corp. CA 92610). Signals were subsequently digitized at 2 kHz (PCI-63203, National Instrument Corp. Austin, TX, USA) and transmitted to a custom laboratory software which controlled stimulus delivery and MEP acquisition. For stimulation, participants were fitted with a Waveguard™ TMS compatible EEG cap (ANT Neuro, Madison, WI, USA) to guide coil placement and a u-shaped neck cushion was used to maintain head position and prevent neck fatigue. TMS was applied sequentially on each hemisphere using a predetermined and counterbalanced order. For each hemisphere, the hot-spot for the FDI was first determined by determining the site where MEPs could be evoked at a minimal intensity with the coil held tangentially on the scalp at approximately 45° in the mid-sagittal plan. This site was marked with a sticker. Then, the resting motor threshold (RMT) was determined using a software tool (Motor Threshold Assessment

Tool[1] 2.0) developed by Borckardt et al. (2006). The MTAT involves a pre-set stimulation pattern to track the threshold intensity on the assumption that there will be no response (no MEP) for a subthreshold stimulus and a successful MEP (i.e., amplitude ≥50μV) for a suprathreshold stimulus. With this technique, the RMT can be reliably estimated with a 95% confidence following 14-17 stimuli. Once determined, the stimulator intensity was set at 110% of RMT and 15 MEPs were recorded to get a baseline value. In all sessions, the coil was held by the same experienced investigator (FT) to ensure consistent placement. All experiments were performed between 9 am and 4 pm to avoid diurnal variations in excitability (Doeltgen and Ridding 2010).

Task-Related Variations in Corticospinal Excitability

To assess task-related modulation, participants were presented with short video sequences (6 s, instructions: 2.25 s; task, 3.75 s). The videos were displayed on a CRT monitor (42.5 cm, Viewsonic GS771, Brea, CA, USA) placed about 1 m in front of the participant at eye level. As shown in Fig. 1, the video sequences consisted of four different task conditions: (1) Silent Counting task (Sil_Count), (2) right-hand judgment (RHJ), (3) left-hand judgments (LHJ), and (4) Foot Observation (Foot_Obs). For the Sil_Count task, participants were instructed to count backward in their head from a predetermined random number comprised between 20 and 99 and to report which number they reached when the trial ended. The Sil_Count task was included as a means to test the selectivity of modulation with respect to differences in task domains (i.e., primary motor imagery vs. numerical processing). For laterality judgments, participants were presented with hand stimuli similar to those used for training with the HLT but depicting different postures and orientations to avoid repetition since all the images used in the

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[1] http://www.clinicalresearch.org/sorfware.htm

videos were taken from the Recognise™ Flash Cards right/left discrimination.[2] One set of videos (n=12) presented images depicting a left hand (i.e., LHJ), while the other set (n=12) presented images depicting a right hand (i.e., RHJ). In each series of videos, the images selected represented a mix of hands in different postures with about one half depicting a dorsal view (11/24) and the remaining, a palmar view (13/24). For the Foot_Obs task, participants were simply instructed to observe an image depicting a barefoot (left). The latter condition provided a control to account for possible variations in excitability associated with observation of body parts and also to control for subtle modulation due to context-dependent effects owing to testing conditions (Bestmann and Krakauer 2015). As stated earlier, the time point for TMS delivery during the videos was individualized for each participant on the basis of his/her performance in the HLT, as tested with the Recognise™ app. Thus, for each participant, custom software was used to set TMS triggering at a specific frame in the video sequence, which frame corresponded to a time point equivalent to half of the MRT recorded during performance of the HLT. Such delay was in line with event-related potential studies showing that maximal frontal and parietal activity is detected at a later stage of processing (600-900 ms) when participants are engaged in mental rotation tasks (Thayer et al. 2001; Thayer and Johnson 2006). The same time point for TMS delivery was used in the other videos/conditions. For TMS testing, each trial consisted of the presentation of a video sequence (see Fig. 1) which corresponded to one of the four conditions (i.e., Sil_Count, RHJ, LHJ, Foot_Obs). Each video was presented 12 times for a total of 48 trials/hemisphere (i.e., 12 MEPs/condition) using a predetermined random order, which was different for each hemisphere. The test intensity of TMS was set at 110% of the RMT for all participants.

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[2] Hand images reproduced from Recognise™ Flash Cards with permission of the Noigroup Publications (Adelaide, Australia).

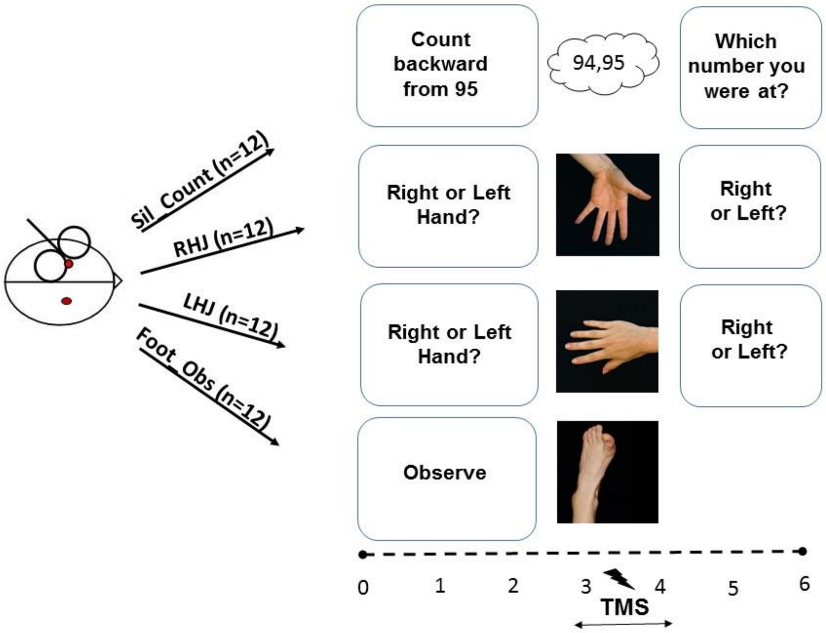

Fig. 1 Schematic representation of the experimental paradigm. During testing, participants were presented with short video sequences (6 s, n=48) according to a predetermined random order. One set of videos asked participants to silently count backward in their head from a given number displayed on-screen (Sil_Count). Another set presented images depicting right hands to judge on their laterality (i.e., right-hand judgment RHJ). A similar set of videos presented images of left hands (i.e., left-hand judgment, LHJ). One last set of videos asked participants to simply observe the image of a left foot (Foot_Obs). While participants were watching, a transcranial magnetic stimulation (TMS) pulse was delivered at ~3 to 4 s delay during the presentation to test corticospinal excitability. Although TMS is shown only for the left hemisphere, both were tested sequentially. Hand images in the videos were reproduced from Recognise™ Flash Cards with permission of the NOIgroup Publications (Adelaide, Australia).

Data Analysis and Statistics

Performance data in the HLT regarding MRT and mean accuracy were obtained directly from the Recognise^{TM} app for each participant. MEP data were analyzed off-line to measure their amplitude (peak-to-peak) using a script developed with MATLAB® for each trial in each condition to derive mean values for individual participants. Task-related variations in corticospinal excitability were first examined by expressing MEP amplitude measured in each task condition relative to baseline to get MEP ratio (i.e., MEP_{task}/MEP_{BL} X 100). The ratios provided a general index to assess the level of task-related modulation when compared to baseline resting excitability. However, for statistical comparisons, only variations in absolute MEP amplitude measured across task condition were considered. After verifying the normality of distribution (D'Agostino and Pearson test), individual MEP values in µV were entered into a 2 X 4 ANOVA with "Hemisphere" (left vs. right) and "Condition" (Sil_Count, Foot_Obs, RHJ, LHJ) as the repeated factors. Post-hoc tests were performed using the Sidak's multiple comparisons test. The significance level was set at $p < 0.05$. All tests and graphics were performed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, California USA, www.graphpad.com).

Results

Hand laterality task

In general, participants were quite apt at discriminating hand laterality as judged by the performance of the Recognition™ app with an overall mean accuracy of 86% correct (range, 67-98%) and an MRT of 2.2 s (range, 1.3-4.1 s). Based on this performance, the TMS pulse was delivered on average at 3.30 s (range 3.10 -3.61 s) in the course of the video sequence to test corticospinal excitably, i.e. on average at 1.1 s (range 0.9-1.4 s) after the hand image appeared on-screen.

Task-Related Modulation of Corticospinal Excitability

The mean test intensity (equivalent to 110% RMT) to assess corticospinal excitability in the left and right hemisphere was respectively 52 ± 12.5 and 54.7 ± 11.7 % of stimulator output. Figure 2 illustrates a typical example of modulation in MEP amplitude associated with the different task conditions. Two main observations can be made by inspecting Fig. 2. First, it can be seen that task-related variations in MEP amplitude tended to be comparable between hemispheres, with some exceptions for MEPs in the right hemisphere. Second, with regards to differences between task conditions, indication of MEP facilitation relative to baseline was apparent only for the Sil_Count task. Figure 3a shows the mean variations with respect to baseline measured across task conditions for all participants. In this figure, the lack of strong hemispheric effects as well as the selective effect of Sil_Count task on MEP facilitation can be further appreciated. The fact that task-related modulation did not differ significantly between hemispheres was confirmed by the ANOVA ($F_{1,17}$=2.2, p=0.16) along with the main effect of "Conditions" ($F_{3,51}$ =14.3, p<0.001). No interaction was detected, however ($F_{3,51}$ =1.0, p=0.44). As expected, the effect of "Conditions" was largely attributable to the facilitation observed during the Sil_Count task, which was significantly different from the other three task conditions (p<0.01, Sidak's post-test). Of note, however, and as evident in Fig. 3a, is the clear lack of MEP modulation associated with RHJ and LHJ and this, in spite of the fact that participants correctly identified hand laterality 99% of the time (mean accuracy, LHJ, 99.3 ± 2.1%; RHJ, 99.2 ± 1.0%). Such observations prompted the performance of a secondary experiment to investigate further modulation in corticospinal excitability associated with laterality judgments.

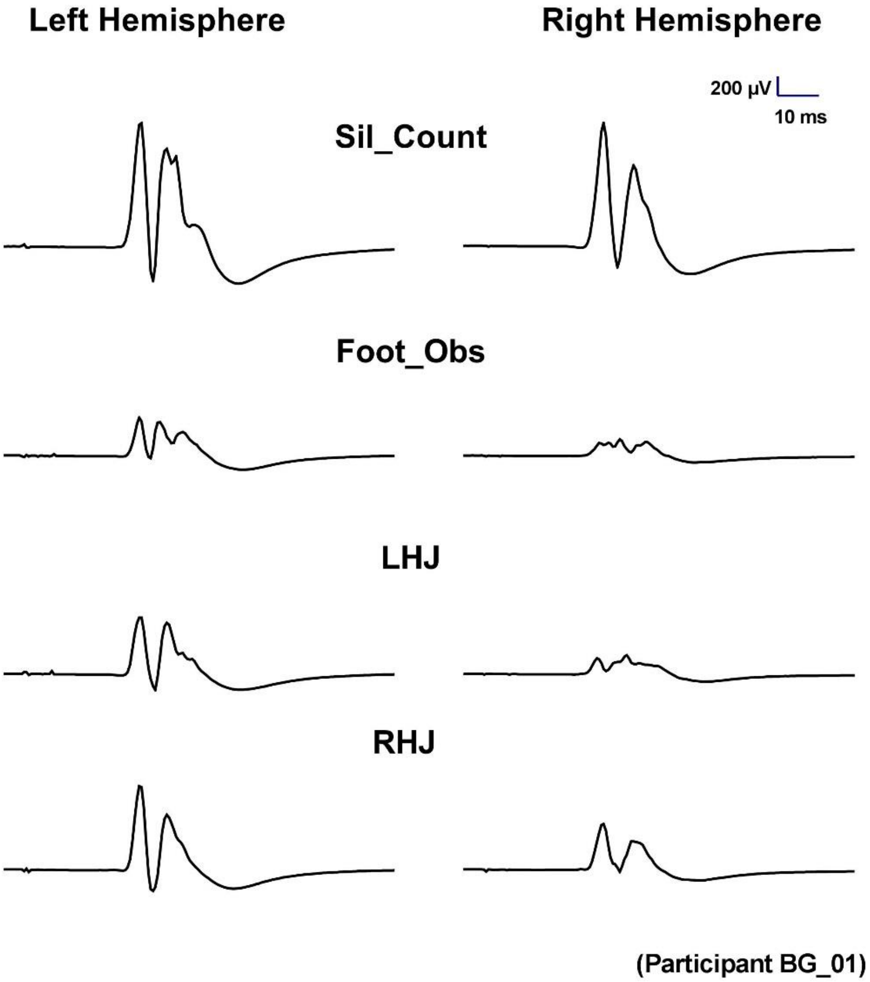

Fig. 2 An individual example of motor evoked potentials (MEPs) recorded from the first dorsal interosseous muscle (FDI) in each hemisphere and across task conditions. Each trace represents an average of 12 responses recorded under each task condition: *BL* baseline, *Sil_Count* silent counting, *Foot_Obs* foot observation, *LHJ* left-hand judgments, *RHJ* right-hand judgments.

Secondary Experiment

Given the failure to detect modulation with respect to laterality judgments in the primary experiment, we performed a secondary experiment on a subset of participants (n=6, 3 males). The protocol to examine variations in corticospinal excitability was largely similar to that used in the primary experiment except for three major differences. First, the images used the videos (12 right hands, 12 left hands) were changed to show images depicting hands performing actions[3] (e.g., hand playing guitar, hand grasping a door knob), the goal being to elicit a greater engagement of the motor system. Second, MEPs were recorded from more proximal wrist muscles and targeted the Extensor digitorum communis (EDC) and Flexor carpi radialis (FCR) muscles to probe modulation in excitability in a motor representation more specifically involved in actual hand rotations (i.e., as compared to FDI). Finally, given that no hemispheric effects were detected in the primary experiment, MEPs were recorded only from the left hemisphere. Like in the primary experiment, the timing of TMS delivery was based on the participant's performance in the HLT (i.e., 3-4 s in the course of the video). A similar analysis was also performed on MEP amplitude data except that MEPs for both right and left laterality judgments were combined to get a single mean value. The mean variations in MEP amplitude computed relative to baseline is shown in Fig. 3b for both the EDC and FCR. It can be seen that the pattern of modulation in both muscles was quite similar to the one observed in the primary experiment. A Friedman's test revealed a significant difference ($p < 0.05$, Freidman statistic > 7) between conditions for both EDC and FCR. Much like in the primary experiment, post-test analysis with the Dunn's test revealed that MEPs in the Sil_Count task were significantly different than those in the Foot_Obs condition for both EDC ($p = 0.03$) and FCR ($p = 0.01$). No other significant

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[3] Hand images were also reproduced from Recognise™ Flash Cards with permission of the Noigroup Publications (Adelaide, Australia).

differences were detected. Thus, overall, the pattern of MEP modulation in this experiment was very similar to that seen in the primary experiments.

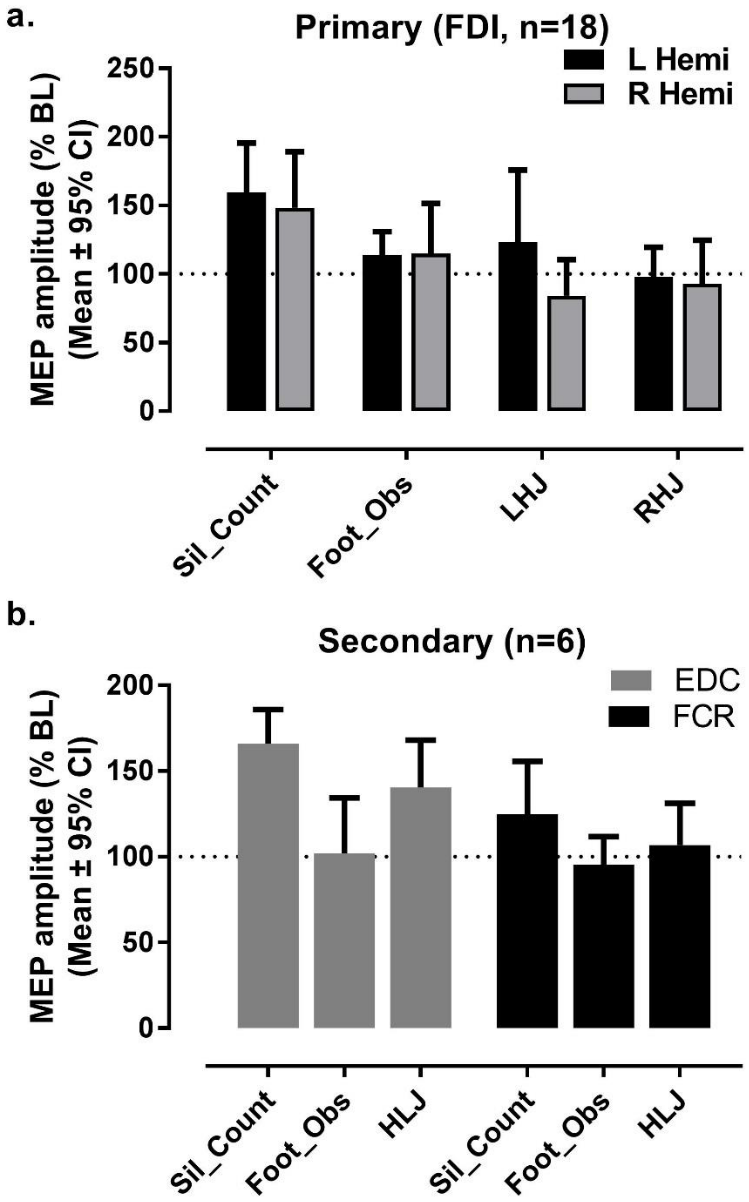

Fig. 3 Comparison of the mean task-related variations in MEP amplitude and the associated 95% confidence interval (CI) computed in the primary (**a**) and secondary experiments (**b**) for all participants and expressed relative to baseline (dotted line). In **a**, the mean variations are shown for each hemisphere for the FDI muscle. Note the presence of MEP facilitation evident only for Sil_Count task and the relative lack of hemispheric effect. In **b**, the mean variations are shown for the extensor digitorum communis (EDC) and flexor carpi radialis (FCR), respectively. Again, note the presence of MEP facilitation for the Sil_Count task. Note that HLJ refers to laterality judgments combined for both right and left-hand stimuli.

Discussion

In this study, we used TMS to examine the involvement of M1 in mental rotations associated with hand laterality judgments performed in conditions similar to those provided in a commercial application designed for right/left discrimination of body parts. We hypothesized that laterality judgments would lead to greater MEP facilitation when compared to a mental counting task or a control task. Also, we anticipated that facilitation associated with laterality judgments would be greater in the right hemisphere. Contrary to our first hypothesis, we did not observe MEP facilitation with laterality judgments; significant facilitation being detected only for the counting task. No evidence of hemispheric effects was detected either regarding laterality judgments. A secondary experiment involving a different set of hand images to judge and probing a more proximal motor representation yielded the same results. In the next section, we will examine the significance of these negative findings in the light of the current literature on motor facilitation associated with motor imagery tasks and their implication for rehabilitation.

Laterality Judgments and (lack of) Modulation in Corticospinal Excitability

Before addressing the reasons as to why TMS responses were little affected by laterality judgments, it is important first to ascertain whether the experiment conditions were optimal to detect subtle modulation associated with mental rotation. In this regard, we have several reasons to believe that our conditions were optimal. First, our group of participants was naïve with regards to laterality tasks and thus likely free of any prior cognitive bias in discriminating right/left body parts. Second, our hand stimuli for both training and testing consisted of high-quality images depicting real hands in different postures with a balance of back and palmar views, which were reproduced from a commercial software specifically designed for training right/left discrimination. Third, the time point to test variations in corticospinal excitability during task performance was individualized for each participant and corresponded to delays reported for mental rotation processes (Thayer and Johnson 2006). Fourth, as indicated by the high performance, our participants were fully engaged with the task when it came to laterality judgments. Finally, the fact that reliable MEP facilitation was detected in the other mental task (Sil_Count) further attests to the validity of our experimental paradigm in detecting subtle variations in corticospinal excitability.

If the conditions were indeed optimal and participants engaged with the task, why then the failure to detect MEP modulation with laterality judgments? One possibility in this regard is that participants became rapidly familiar with the set of images to judge after being exposed to similar images during the training phase with the Recognise™ app, even though a different set was used during testing. Owing to this sense of familiarity, judging hand laterality during the videos might have become too easy, thereby reducing the necessity for mental rotations. Although we cannot rule out this possibility, it seems unlikely given that participants did not comment on the laterality task being easier in the videos than during training with the app. It is true that the laterality judgments in terms of accuracy did seem to improve between training and testing phases, but this improvement simply reflected the fact that judgments during testing were less constrained than during training; participants being instructed to provide verbal reports at the end of the trial instead of being asked to report as fast as they can. Even admitting that familiarity did have an influence, such factor could hardly account for the lack of modulation observed in the secondary experiment, where an entirely different set of images was used in the videos and for which participants had no prior exposure.

In fact, findings from both the primary and secondary experiments suggest that participants likely relied on alternative strategies to judge hand laterality with probably less involvement of motor processes, thus explaining the absence of modulation. In this respect, our results are in line with other reports where the role of the M1 in mental rotations involved in laterality judgments has been questioned (Sauner et al. 2006; Thayer and Johnson 2006; Bode et al. 2007). As noted earlier, the assumption that implicit motor imagery is the “default” strategy used when making laterality judgments on body parts needs to be pondered by evidence that sometimes participants may rely on alternative strategies. For instance, King et al. (2015) reported on the case of a female patient with chronic foot pain who relied on 3rd person perspective, and thus visual imagery strategy, to perform laterality judgments with a high-level of accuracy. Vannuscorps et al. (2012) reported similar observations about a patient whose performance in judging laterality was as accurate as controls in spite of a congenital limb absence, indicating that such judgments can be performed only on the basis of visual cues. Along the same line, Logie et al. (2011) compared brain activation patterns in high and low imagers during mental rotation of 3D objects and concluded that the two groups used different imagery strategies to perform the task, with high imagers using an external strategy (object-based rotation) associated with activation in premotor and visual areas whereas low imagers used a more internal strategy (viewer-based rotation) associated with activation in visuospatial processing areas and the SMA. For these authors, such findings strengthened the notion that confronted with the same mental rotation task participants may rely on different cognitive strategies (and neural activation patterns) to achieve a similar behavioral result. In agreement with this, Lebon et al. (2012) reported on their observations of “Imagers” and “Rotators” who displayed differential modulation in corticospinal excitability when tested in the context of either an explicit motor imagery task (thumb movements) or an implicit motor imagery task (mental rotation task similar to the current task). The former exhibited preferential facilitation of MEPs during the imagery task but not during rotation task, whereas the latter exhibited the opposite pattern of modulation. Interestingly, and much like in the present study, these authors did not find task effects when comparing overall variations in MEP amplitude; an absence they attributed to differences between “imagers” and “rotators”. Here, we did not perform such regrouping of our participants since our task conditions did not allow us to contrast between implicit and explicit motor imagery. Beyond individual preferences and abilities, another factor that might have influenced the strategies used to judge laterality are related to hand stimuli characteristics. As we have alluded to earlier, our set of hand images consisted of bare hands in different postures with a balanced number of back views and palmar views. Previous studies (Steenbergen et al. 2007; Habacha et al. 2014) have shown that both the perspective and orientation of the hands depicted as stimuli can exert influence on the types of strategies used to judge laterality. For instance, when judging hands presented from a back-view perspective, motor imagery is apparently little involved in right-left discrimination (Steenbergen et al. 2007). This perspective effect was confirmed recently by Zapparoli et al. (2014), who compared both performance and brain activation levels when judging hand stimuli presented either with a back-view or a palmar view. Their results revealed faster judgments for hands presented with a back-view perspective, which was associated with stronger activation in visual areas. In contrast, judging hands from a palmar view perspective elicited slower responses and stronger activation in premotor and parietal cortices. These findings confirmed that visual strategies are likely predominant when judging hand laterality from a “familiar” perspective, whereas motor imagery and mental rotations would be predominant when viewing hands in less familiar perspectives. Although we did not specifically examine the impact of hand stimuli orientation in this study, it is possible that this factor might have contributed to the lack of consistent modulation, participants unknowingly opting for a simple visual strategy when judging hands presented from a back-view perspective. In fact, on debriefing, some participants did report using visual cues based on the thumb localization to judge laterality. To summarize, it seems likely that the absence of MEP modulation in association with laterality judgments reflected the fact that participants used alternative strategies and most notably visual strategies (e.g., 3rd person perspective) to judge laterality, which would have reduced the need for motor simulation and thus M1 engagement.

Corticospinal Facilitation and Mental Counting

One intriguing finding in the present study is the large corticospinal facilitation detected in both hemispheres in association with the counting task. As stated earlier, the inclusion of this condition was to contrast MEP modulation in relation to the specific domain of cognition, namely perceptual-motor imagery vs. numerical processing. In this regard, finding a large and consistent MEP facilitation during mental counting was somehow surprising given that such modulation was expected for the laterality task, as explained above. In a previous study (Clark et al. 2004), we reported our observations regarding a similar comparison across task domains where we found evidence of clear MEP facilitation for motor imagery tasks against the mental counting task. While the present observations may seem at odds with our previous ones, it is important to emphasize the major differences between the two studies regarding task conditions to elicit motor imagery. In particular, the use of live action videos in our previous study coupled with explicit instructions to either observe or image actions likely contributed to elicit greater motor activation; hence the larger MEP facilitation for these tasks over the counting task. It is also worth noting that the counting task in our previous report was also associated with some degree of MEP facilitation with ~50% of participants showing enhanced MEPs. At that time, this facilitation was attributed to nonspecific processes linked with sustained attention (Ortuno et al. 2002). Since then, the evidence has accumulated linking the human motor cortical system with the cortical network involved in numerical processing (e.g., see Andres et al. 2007; Sato et al. 2007; Tschentscher et al. 2012). In general, the notion that cortical areas mediating the production of action might also be critically involved in higher cognitive processes has been linked to the theory of “embodied cognition” (Rumiati et al. 2010). In the case of numerical processing, the interactions between fingers and numbers provide a typical example as to how motor processes could contribute to higher processes since finger counting represents a typically embodied strategy to perform simple calculations. In this regard, both neuroimaging studies (Tschentscher et al. 2012) and neurophysiological TMS studies (Sato et al. 2007) have provided evidence of the strong link between finger counting habits and activation of the M1. Given these recent developments, it is not so surprising to find MEP facilitation in association with a mental counting task. In this regard, our results are in line with the report of Andres et al. (2007), who also found an increase in corticospinal excitability in a silent counting task. Interestingly, these authors also performed a controlled experiment to determine whether the facilitation was related to subvocal speech output since like, in this study, participants had to count mentally in their head. This control experiment confirmed that the observed MEP facilitation was selective to mental counting and not speech related. Thus, we can reasonably assume that the MEP facilitation we observed during the counting task was likely a direct reflection of mental activity and M1 engagement in numerical processing. In addition, considering the nature of our counting task which involved arithmetic (backward counting), it is also likely that the recruitment of other prefrontal (superior frontal gyrus) and parietal (e.g. inferior parietal lobule) regions, thought to be critical for calculation tasks (Arsalidou and Taylor 2011), contributed to enhance M1 excitability during the process via intra-cortical connections.

(Lack of) Hemispheric Effects

In the present study, our predictions regarding hemispheric differences in task-related MEP modulation proved to be wrong. On the one hand, given the failure to detect MEP facilitation, our prediction for an asymmetry for the right hemisphere in relation to laterality judgments could not be fulfilled. As stated in the Introduction, the latter prediction was based on evidence indicating a predominant role of the right hemisphere in processing visual-kinesthetic information (Naito et al. 2005) and, in particular, hand movement-related information (Hagura et al. 2009). Studies that have addressed hemispheric differences in hand laterality tasks have produced rather equivocal evidence with regards to the predominance of one hemisphere over the other. For instance, Tomasino et al. (2005), using a TMS interference approach, reported a critical role for the left hemisphere in laterality judgments relying on mental rotations of hands. Using a similar approach, Pelgrims et al. (2011) could not reproduce these effects and concluded that both right and left M1 were equally involved in hand laterality judgments. While the present findings preclude any conclusion on the issue of hemispheric specialization in hand laterality judgments, the absence of clear hemisphere effects in the observed MEP facilitation would be congruent with the notion that mental rotation tasks rely largely on bilateral activation of prefrontal and parietal areas, as evidenced in neuroimaging studies (Vingerhoets et al. 2002; Thayer and Johnson 2006).

Limitations and Implications

The present study has certain limitations that are worth mentioning. First, as we have argued above, the failure to detect task effects in association with laterality judgments might have reflected in part our selection of hand stimuli, but again our goal was not to test the effect of image orientation on corticospinal excitability. As stated earlier, our testing paradigm to examine the effects of laterality judgments was based on the approach developed for rehabilitation by the NOI Group (http://www.noigroup.com/) with the “Recognition™” app. Second, the fact that our group of participants consisted of healthy young adults is another major limitation which precludes any generalization of our findings to other segments of the population and, in particular, patient populations. While our results may not apply directly to patients, the failure to detect MEP facilitation about laterality judgments has implications for clinical applications of laterality tasks. Indeed, based on our findings, it seems that one cannot assume that the presentation of images depicting hands or feet in different postures to judge on their laterality is sufficient in itself to elicit implicit motor imagery and M1 engagement. Such considerations need to be put in perspective in view of the wealth of evidence (Grospretre et al. 2016), including our own reports (Clark et al. 2004; Leonard and Tremblay 2007), demonstrating a clear M1 involvement and reliable MEP facilitation when participants are provided with engaging task conditions, such as observing live actions or being asked to imagine oneself doing actions.

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General discussion and conclusion

This project started with the simple assumption that making laterality judgments about hand stimuli would elicit clear motor facilitation that could be detected with TMS. As it is often the case in research, our assumption, although based on apparently solid evidence from chronometric and neuroimaging studies, turned out to be too simplistic. In fact, our review of the TMS literature provided the first insights that the assumption linking laterality judgments of body parts with motor imagery was not as clear as it seemed, given the conflicting findings. The current project further adds to the controversial evidence by showing that high performance in judging the laterality of hand stimuli can be performed with seemingly little involvement of the motor system. Clearly, our results indicate that presenting static images depicting hands in different postures to judge, as used in the NOI Recognise App™, is not sufficient in itself to elicit motor simulation. As stated before, the current findings contrast with previous observations from this lab and other reports on motor facilitation associated with motor imagery tasks and highlight the importance of selecting task conditions. The presentation of static images of body parts might not be optimal to elicit motor facilitation and engaging the motor system may require more active conditions like when using videos of live actions. Of course, the story might be different with patients with chronic conditions in the context of rehabilitation, but the present results point to the need to be cautious in assuming that patients will engage in motor simulation just by making judgments about laterality of body parts. We believe it to be crucial that further research emphasizes the importance of investigating the motor imagery of mental rotation with special attention to the aspect of the hand displayed. By gathering these findings, perhaps a clearer picture of the usefulness of laterality tasks in rehabilitation settings can be yielded.

With regards to the issue of differences between hemispheres, our study further highlights the gap between effects reported in neuroimaging studies and those reported in brain stimulation studies.

The fact that we did not find asymmetry in favor of either the right or the left hemisphere in relation to mental tasks (i.e., hand rotation or counting task) just adds another piece of evidence showing that cognitive processes, in general, are highly bilateral in nature. This latter observation reminds us that laterality effects reported in neuroimaging studies, such as fMRI, are often the results of statistical processing and only reflect minor differences in levels of activation. These minor differences may be misleading as they may not be of any practical relevance. It is therefore easy to understand why clear hemispheric differences are not easily detected when examining responses to TMS, which better reflect physiological processes rather than fluctuations arising from statistical comparisons.

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Appendix A: Modified Edinburgh Handedness Questionnaire

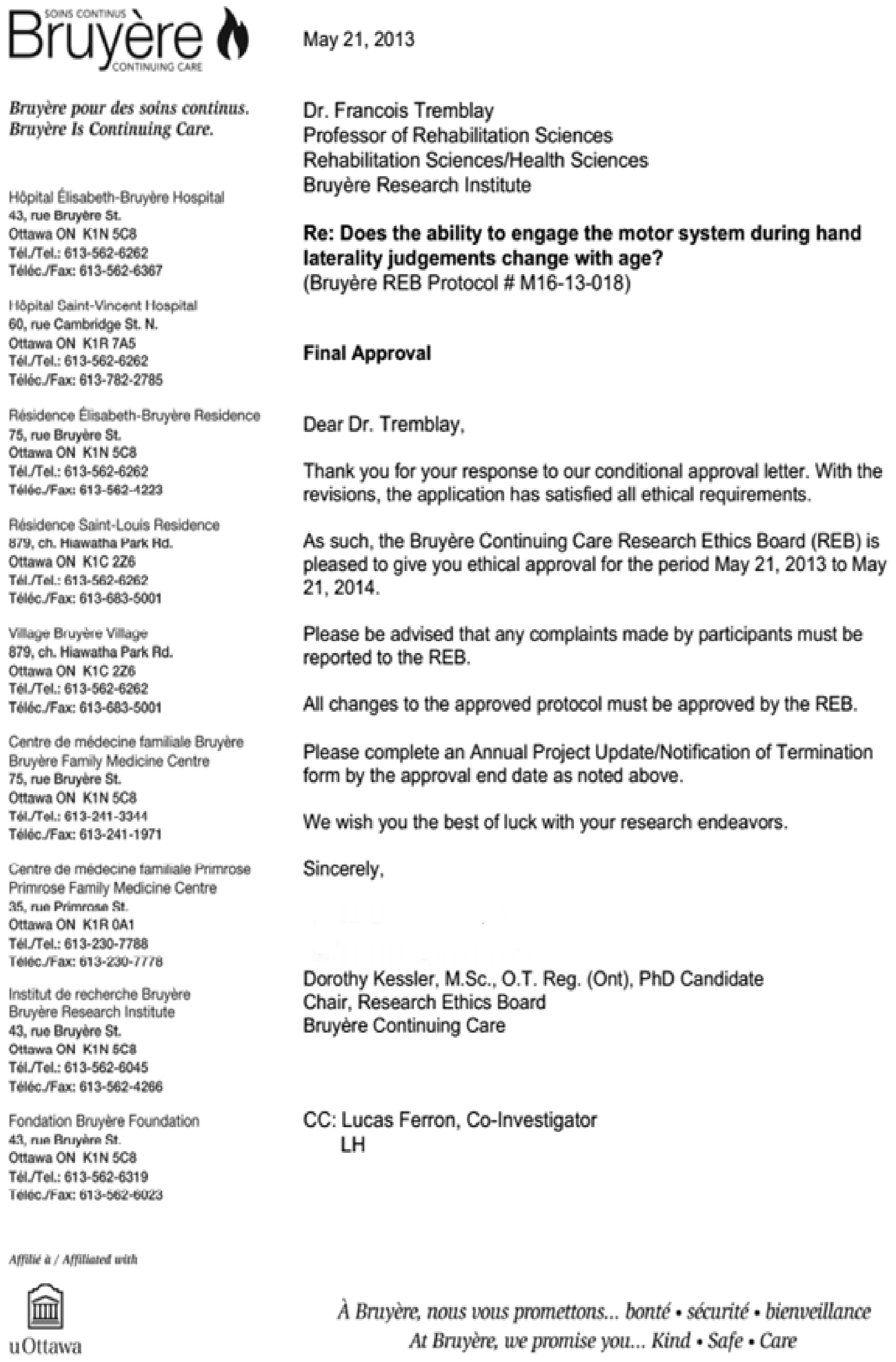
Which hand do you prefer to use when:

	Left	No Preference	Right	Do you ever use the other hand?
Writing:	☐	☐	☐	☐☐Yes
Drawing:	☐	☐	☐	☐☐Yes
Throwing:	☐	☐	☐	☐☐Yes
Using Scissors:	☐	☐	☐	☐☐Yes
Using a Toothbrush:	☐	☐	☐	☐☐Yes
Using a Knife (without a fork):	☐	☐	☐	☐☐Yes
Using a Spoon:	☐	☐	☐	☐☐Yes
Using a Broom (upper hand):	☐	☐	☐	☐☐Yes
Striking a Match:	☐	☐	☐	☐☐Yes
Opening a box (holding the lid):	☐	☐	☐	☐☐Yes
	Additional Items			
Holding a Computer Mouse:	☐	☐	☐	☐☐Yes
Using a Key to Unlock a Door:	☐	☐	☐	☐☐Yes
Holding a Hammer:	☐	☐	☐	☐☐Yes
Holding a Brush or Comb:	☐	☐	☐	☐☐Yes
Holding a cup while Drinking:	☐	☐	☐	☐☐Yes

This handedness questionnaire was adapted by Cohen 2008 from:

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

Appendix B: REB approval



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May 21, 2013

Dr. Francois Tremblay
Professor of Rehabilitation Sciences
Rehabilitation Sciences/Health Sciences
Bruyère Research Institute

Re: Does the ability to engage the motor system during hand laterality judgements change with age?
(Bruyère REB Protocol # M16-13-018)

Final Approval

Dear Dr. Tremblay,

Thank you for your response to our conditional approval letter. With the revisions, the application has satisfied all ethical requirements.

As such, the Bruyère Continuing Care Research Ethics Board (REB) is pleased to give you ethical approval for the period May 21, 2013 to May 21, 2014.

Please be advised that any complaints made by participants must be reported to the REB.

All changes to the approved protocol must be approved by the REB.

Please complete an Annual Project Update/Notification of Termination form by the approval end date as noted above.

We wish you the best of luck with your research endeavors.

Sincerely,

Dorothy Kessler, M.Sc., O.T. Reg. (Ont), PhD Candidate
Chair, Research Ethics Board
Bruyère Continuing Care

CC: Lucas Ferron, Co-Investigator
LH

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Appendix C: Title page of the manuscript

(Lack of) Corticospinal facilitation in association with hand laterality judgments

Lucas Ferron & François Tremblay

Experimental Brain Research

ISSN 0014-4819

Exp Brain Res
DOI 10.1007/s00221-017-4973-9

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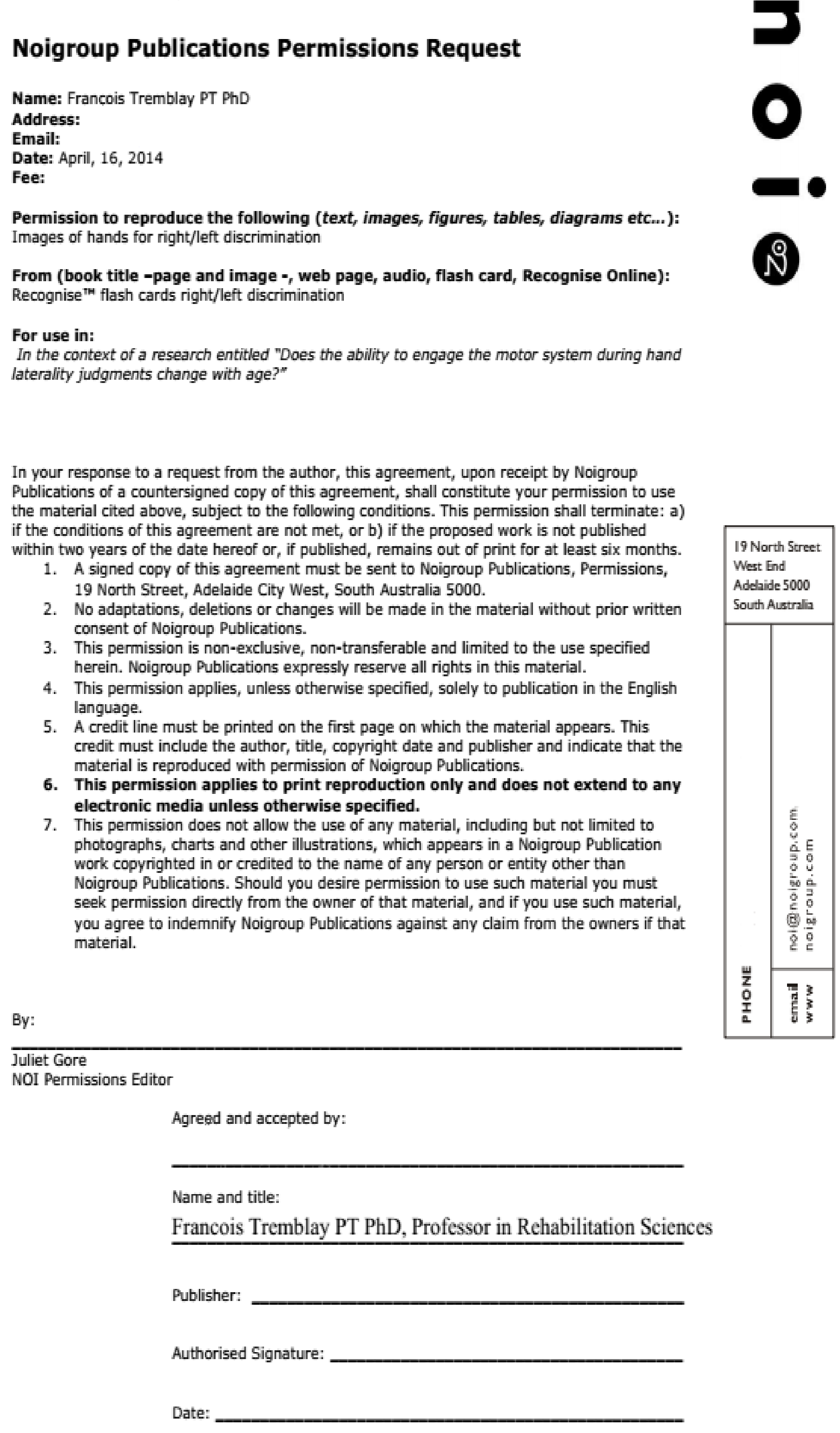
Appendix D: NOI group permission



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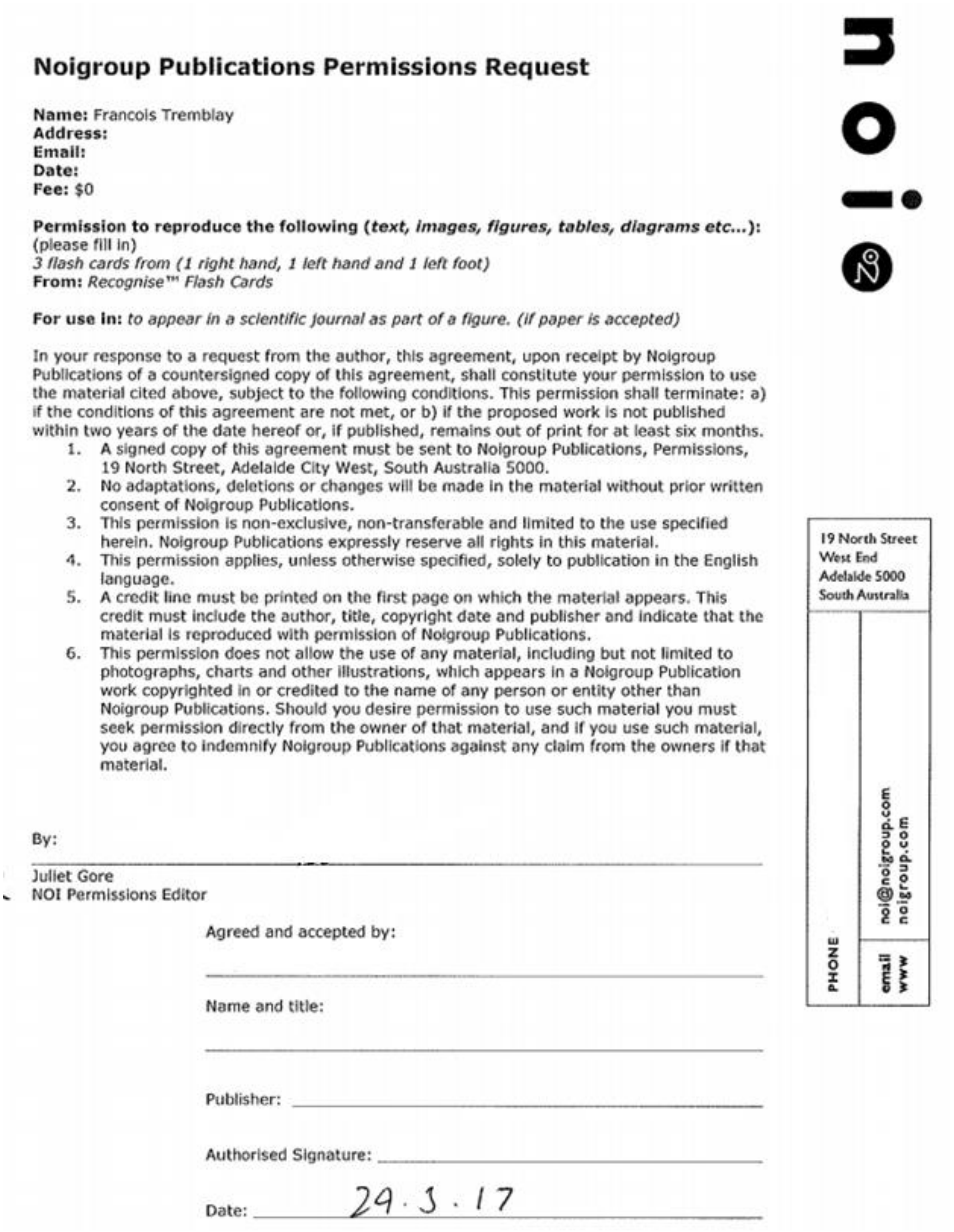

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