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VALIDATION OF A MODEL OF SENSORIMOTOR INTEGRATION WITH CLINICAL BENEFITS

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VALIDATION OF A MODEL OF SENSORIMOTOR INTEGRATION WITH CLINICAL BENEFITS

Thèse de doctorat en Neurosciences

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par

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pour Le Doyen
de la Faculté de Biologie et de Médecine

Prof. Christine Mohr

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To all of you, and any I might have forgotten, Thank you.

Abstract (English)

Healthy sensorimotor integration – or how our touch influences our movements – is critical to efficiently interact with our environment. Yet, many aspects of this process are still poorly understood. Importantly, several movement disorders are often considered as originating from purely motor impairments, while a sensory origin could also lead to a similar set of symptoms. To alleviate these issues, we hereby propose a novel biologically-based model of the sensorimotor loop, known as the SMILE model. After describing both the functional, and the corresponding neuroanatomical versions of the SMILE, we tested several aspects of its motor component through functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). Both experimental studies resulted in coherent outcomes with respect to the SMILE predictions, but they also provided novel scientific outcomes about such broad topics as the sub-phases of motor imagery, the neural processing of bodily representations, or the extend of the role of the extrastriate body area. In the final sections of this manuscript, we describe some potential clinical application of the SMILE. The first one presents the identification of plausible neuroanatomical origins for focal hand dystonia, a yet poorly understood sensorimotor disorder. The last chapter then covers possible improvements on brain-machine interfaces, driven by a better understanding of the sensorimotor system.

Résumé (French)

La façon dont votre sens du toucher et vos mouvements interagissent est connue sous le nom d'intégration sensorimotrice. Ce procédé est essentiel pour une interaction normale avec tout ce qui nous entoure. Cependant, plusieurs aspects de ce processus sont encore méconnus. Plus important encore, l'origine de certaines déficiences motrices encore trop peu comprises sont parfois considérées comme purement motrice, alors qu'une origine sensorielle pourrait mener à un même ensemble de symptômes. Afin d'améliorer cette situation, nous proposons ici un nouveau modèle d'intégration sensorimotrice, dénommé « SMILE », basé sur les connaissances de neurobiologie actuelles. Dans ce manuscrit, nous commençons par décrire les caractéristiques fonctionnelles et neuroanatomiques du SMILE. Plusieurs expériences sont ensuite effectuées, via l'imagerie par résonance magnétique fonctionnelle (IRMf), et la stimulation magnétique transcranienne (SMT), afin de tester différents aspects de la composante motrice du SMILE. Si les résultats de ces expériences corroborent les prédictions du SMILE, elles ont aussi mis en évidences d'autres résultats scientifiques intéressants et novateurs, dans des domaines aussi divers que les sous-phases de l'imagination motrice, les processus cérébraux liés aux représentations corporelles, ou encore l'extension du rôle de l'extrastriate body area. Dans les dernières parties de ce manuscrit, nous dévoilons quelques applications cliniques potentielles de notre modèle. Nous utilisons le SMILE afin de proposer deux origines cérébrales plausibles de la dystonie focale de la main. Le dernier chapitre présente comment certaines technologies existantes, telles que les interfaces cerveaux-machines, pourraient bénéficier d'une meilleure compréhension du système sensorimoteur.

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List of abbreviations

ADM	Abductor digiti minimi
BG	Basal ganglia
BMI	Brain-machine interface
Cer	Cerebellum
CSP	Cortical silent period
EBA	Extrastriate body area
ECoG	Electrocorticography
FDI	First dorsal interosseus
FDR	False discovery rate
FDS	Flexor digitorum superficialis
FHD	Focal hand dystonia
fMRI	Functional magnetic resonance imaging
ICMS	Intracortical Microstimulation
M1	Primary motor cortex
MEP	Motor-evoked potential
Par	Parietal cortex
PM	Premotor cortex
rIPL	Right Inferior Parietal Lobule
RT	Response times
S1	Primary sensory cortex
SDT	Spatial discrimination threshold
SMA	Supplementary motor area
SMILE	Sensory-Motor Integrative Loop for Enacting
TDT	Temporal discrimination threshold
Th	Thalamus
TMS	Transcranial magnetic stimulation

1. Introduction and overview

1.1. First steps into sensorimotor integration

We are generally unaware on how much the afferent somatosensation information – originating from our skin and muscles – is critical in directing even the slightest of our movements. Without it, you would probably crush the plastic cup you are sipping from. Even more likely, you would spill all of its content when grasping it, as you might fail to compute the correct trajectory for your hand to reach that glass on the table. As a last example, have you ever considered the amount of information required simply to keep you standing? Equilibrium relies on the combination of a handful of sources, such as skin pressure on the soles of your feet, tension from each of your legs and chest muscles, and balance information from your inner ear, into an estimation of the state of your whole body in space. Based on this, your brain can constantly and unintendedly update your muscular activity to correct your stance. As you can see, this mechanism involves a continuous loop of motor-sensory-motor processes.

Indeed, the accurate performance of movements requires several sequential yet interconnected mechanisms, namely motor preparation, execution and monitoring (Wolpert and Ghahramani, 2000). The first two are coded by the motor system, while the monitoring feedback is processed by the sensory systems (Peterka, 2002). Sensorimotor integration is the interplay between these two systems, with the motor section achieving the role of effector by constantly actuating the state of the body, while the sensory system continuously monitors the results. The natural combination of sensory inputs and motor outputs results in the ability to coherently organize bodily sensations and motor responses. Only when both motor and sensory information are properly integrated in this reciprocal feedback loop, can overt movements be successfully and properly performed.

1.2. Modeling the sensorimotor system

Aberrant behaviors occurring within the sensorimotor loop can result in a broad panel of movement disorders. One of such disorders is focal dystonia, a hyperkinetic alteration usually characterized by abnormal movement and/or postures of a specific body part, in the absence of other basic motor impairments (Fahn et al., 1998). Despite the essential influence of sensorimotor integration mechanisms on daily life, many unknowns remain on the general principles of its healthy and pathological anatomic-functional organization. To unravel this issue, in the present thesis, we

first propose a novel bio-computational model of sensorimotor integration: the Sensory-Motor Integrative Loop for Enacting (SMILE), based on the available data from experimental psychology, neurophysiology, and neuroimaging. The goal of this model is to provide a new tool to test hypotheses on the sensorimotor system, translate them into empirical investigations and clinically relevant questions, and implement novel intervention protocols for rehabilitation in the framework of sensorimotor disorders.

In the first part of the present thesis, we will introduce the SMILE with a special concern on the description of both its functional and neuroanatomical versions, and how to integrate them together. The following two chapters present two experimental studies aiming at investigating and validating various aspects of the SMILE, using different imaging modalities, namely functional Magnetic Resonance Imaging (fMRI), and Transcranial Magnetic Stimulation (TMS).

1.3. Motor imagery to dissociate sensory and motor mechanisms

To test such a complex interconnection of processes, one approach consists to isolate its smallest indivisible constituents and investigate them separately. In the case of sensorimotor integration, one can for example attempt to segregate the sensory component from its motor counterparts. One elegant approach toward this aim is granted by motor imagery, which embraces motor processes without generating the corresponding sensory feedback inherent to overt movements. This is made possible by the concept of functional equivalence, binding not only motor imagery, but also the other variants of imagery (such as visual imagery, for example). Functional equivalence states that the neural correlates linked to the imagination of a movement grossly correspond to the actual, overt performance of the same action (Jeannerod, 2001, Munzert et al., 2009). Strictly speaking, this means that the same areas of your brain will be responsible for waving, whether you actively perform the movement or simply imagine it. Furthermore, motor imagery is composed of the same stages as overt movement, namely planning/preparation, and execution (Jeannerod and Decety, 1995), and present a temporal correspondence in healthy subjects (Georgopoulos and Massey, 1987). Motor imagery is therefore an outstanding approach to investigate the SMILE.

To elicit such motor imagery in the two experimental studies presented in this thesis, we used a prominent cognitive task known as the *Hand Laterality Judgment* task. In this task, participants are requested to identify the laterality of a hand visually presented in different views (for example palm and dorsum) and rotation angles (Cooper and Shepard, 1975, Parsons, 1994). Solving this task requires the unconscious access to motor representations. The rationale of this motor involvement,

corroborated by neuroimagery (Parsons et al., 1995, de Lange et al., 2005), posture modulation experiments (Ionta et al., 2012, Ionta and Blanke, 2009, Ionta et al., 2007, de Lange et al., 2006, van Nuenen et al., 2012) and studies in clinical populations (Fiorio et al., 2006, Helmich et al., 2007), is proposed to arise from the recruitment of an imaginary movement of the corresponding limb from the actual proprioceptive position into the one of displayed stimulus (Parsons, 1994, Parsons, 1987). Remarkably, this task is known as an *implicit* motor imagery task, since participants are usually unaware of relying on motor simulation to solve it. This involvement of the motor system while performing these mental hand rotations has been extensively documented. Compared with the Shepard's rotation task (in which the rotated stimuli are not hands, but three-dimensional objects), it has been showed that RTs are lengthened not only by increasing rotation angles, but is also sensitive to biomechanical constraints. Indeed, response times (RTs) exhibit a clear increase when the stimulus is presented in an anatomically awkward position, such as the finger pointing away from the body midsagittal plane (Cooper and Shepard, 1975, Parsons et al., 1995).

1.4. Experimental studies of this thesis

In the first experimental study (Study A, page 11) we used functional Magnetic Resonance Imaging (fMRI) to investigate the effects of sensorimotor or visual reference frame on local (hands) versus global (full-body) bodily representations. In this paradigm, the hand stimuli could be presented either in isolation, or attached to a full-body. A precedent behavioral study suggests that these contextual contingencies can trigger the recruitment of motor versus visual strategies, based on the perspective implied by the stimulus (Ionta et al., 2012). On this basis, we hypothesized that the recruitment of a specific reference frame could be reflected in the differential activation of sensorimotor or visual brain networks. By directly comparing the brain activities associated with mental rotation of hands or full-bodies, we were able to highlight two different networks of neural correlates associated with local and global bodily representations. Mental rotation of hands recruited more strongly a broad subset of the sensorimotor network, namely the supplementary motor area, premotor cortex, and secondary somatosensory cortex. Conversely, mental rotation of full-bodies presented stronger activity in temporo-occipital regions associated with visual processing, including the functionally-localized extrastriate body area (EBA). Three main outcomes could be obtained from this experiment. First, bodily representations can be carried out by either sensorimotor or visual frames of reference, depending on the stimulus context. Secondly, those two frames of references were processed via distinct brain network, encoding local or global bodily representations. And third, EBA does not exclusively consist of a perceptual node, but also incorporates representational

information of the body. With respect to the SMILE model, this experiment illustrated that it is indeed possible to separate the sensory and motor components of the sensorimotor integration process via specific cognitive tasks, but the fMRI results did not show any significant activity in the primary motor cortex (M1), which, according to the SMILE, has to be integrated in the motor processing loop. To investigate this oddity in particular, we developed our second experimental study (Study B, page 13).

In this latter, we investigated the involvement of M1 during implicit motor imagery via TMS, potentially more prone to identify M1 activations than fMRI, in particular in the case of transient processes. Notably, the question of M1 participation in implicit motor imagery still raises many controversies. In the past two decades, dozens of studies have alternatively confirmed (see for example Kosslyn et al. (1998), Ganis et al. (2000) or Tomasino et al. (2005)) or refuted its participation (see for example Kosslyn et al. (2001a), de Lange et al. (2005), or Sauner et al. (2006)). In TMS studies, we claim that this dissension might be the results of a poor phase-locking of the TMS pulse with the transient mental rotation process hypothetically happening within M1. This failure of phase-locking could be emerging from the high intra- and inter-subject variability of response times. Therefore, in this paradigm, we propose a novel approach for trial normalization in which the timing of the TMS stimulation is adjusted with respect to the expected subject- and stimulus-specific response time. Thanks to this novel paradigm, we were able to identify a specific time-window, spanning from 55% to 85% of the trial duration, during which the excitability of M1 was modulated by different features of the stimuli in mental rotations of hands. This would indicate that part of the motor imagery information at the very least transits via the primary motor cortex. Additionally, it also represents an utterly innovative approach to investigate the different sequential stages of the implicit motor imagery process.

1.5. Clinical applications of the SMILE

The general discussion of this thesis will consider two examples on how the SMILE model can be deployed into clinical settings, to formulate and test hypotheses. In the first part (page 29), we examine a specific sensorimotor disorder, namely *focal hand dystonia* (FHD). After reviewing the prevailing knowledge on symptomatic and pathophysiological mechanisms, we use the SMILE model to distinguish two potential neural sources for dystonia. In the final section of this thesis (page 47), we discuss how a proper understanding of the sensorimotor system can greatly enhance the outcomes of another type of clinical therapy. When a patient suffers an intractable rupture of the central-to-periphery communication – such as following a spinal cord injury – one of the ultimate

resort consists in brain-machine interfaces (BMI). These systems can (among other applications) use signals recorded from the central and/or peripheral nervous system, bypass the lesion, and stimulate the target limb. Alternatively, the decoded neural signals can be used to control an external actuator, being a robotic limb, a wheelchair, or more generally any computerized system. But despite BMIs providing impressive opportunities and promising to restore lost sensorimotor functions, their presence outside of a controlled environment remains highly anecdotal. Based on users' reports, one of the reasons for the failure of this laboratory-to-homes technology transfer lies in the *feel* of those systems. Users simply fail to integrate the BMI into their own body representation, resulting in unnatural impressions and rendering it challenging to control. To overcome this limitation, nowadays cutting-edge BMI advances are guided by the principle of biomimicry; i.e. the artificial reproduction of normal neural mechanisms. In this chapter, we discuss how the integration of biomimetically-driven somatosensory feedback into these systems could critically improve their incorporation into the user's body representation, ultimately leading to a feeling of ownership of the BMI, and greatly improving its performances.

2. A new model: the Somatosensory Integrative Loop for Enacting (SMILE)

The effective performance of movements in everyday life is crucial to be able to adequately integrate our environment and interact with it. Models of the sensorimotor integration have been developed on many different facets, and with widely different purposes. In robotics for example, one might need such a biologically-based model to infer the correct limb movements of an animatronic or humanoid robot (Hauser et al., 2011, Ijspeert, 2008). In the field of cognitive neuroscience, one of the seminal computational models of sensorimotor control was initially developed by Daniel M. Wolpert in the nineties (Wolpert et al., 1995) , and has been thoroughly improved over the years (Franklin and Wolpert, 2011, Wolpert, 1997, Wolpert and Ghahramani, 2000).

Nevertheless, for the clinical understanding of sensorimotor-related disorders, such a comprehensive model of the sensorimotor integration is still missing, in particular upon the reciprocal interplay between sensory inputs and motor outputs. These disorders can manifest as impairments in the control of voluntary actions and unsuccessful interactions with our environment. Potentially, they may arise from an inadequate sampling of sensory events from our surroundings because of a disruption of the normal function of the sensorimotor cognitive processing. As stated earlier, this is where the convenience of motor imagery in dissociating sensory and motor processes is revealed, as it allows to investigate those two components separately. This experimental approach is particularly important for studying the physiology of pathological conditions characterized by sensory-motor integration deficits but without impairments in basic motor functions, such as focal dystonia.

2.1. Functional SMILE

One of the challenges of developing such a model in the context of clinical neuroscience is to enable the model to explain the causal link between dysfunctional brain networks and specific clinical phenotypes. Most prevailing computational models of sensory-motor integration (Shadmehr and Krakauer, 2008, Sanger and Merzenich, 2000, Wolpert et al., 1995) agree on the necessity of one or more nodes dedicated to the motor preparation stage. Building on these existing computational models, we present a biologically-based model of the Sensory-Motor Integrative Loop for Enacting (SMILE). According to SMILE, a functional sensorimotor integration requires the coordination of both low- and high-level nodes. Starting the loop from a voluntary intention to move (or alternatively from a reaction to somatosensory information), the initial signals in the high-level preparation nodes encode the movement planning stage, and they are transmitted to a converter node which will

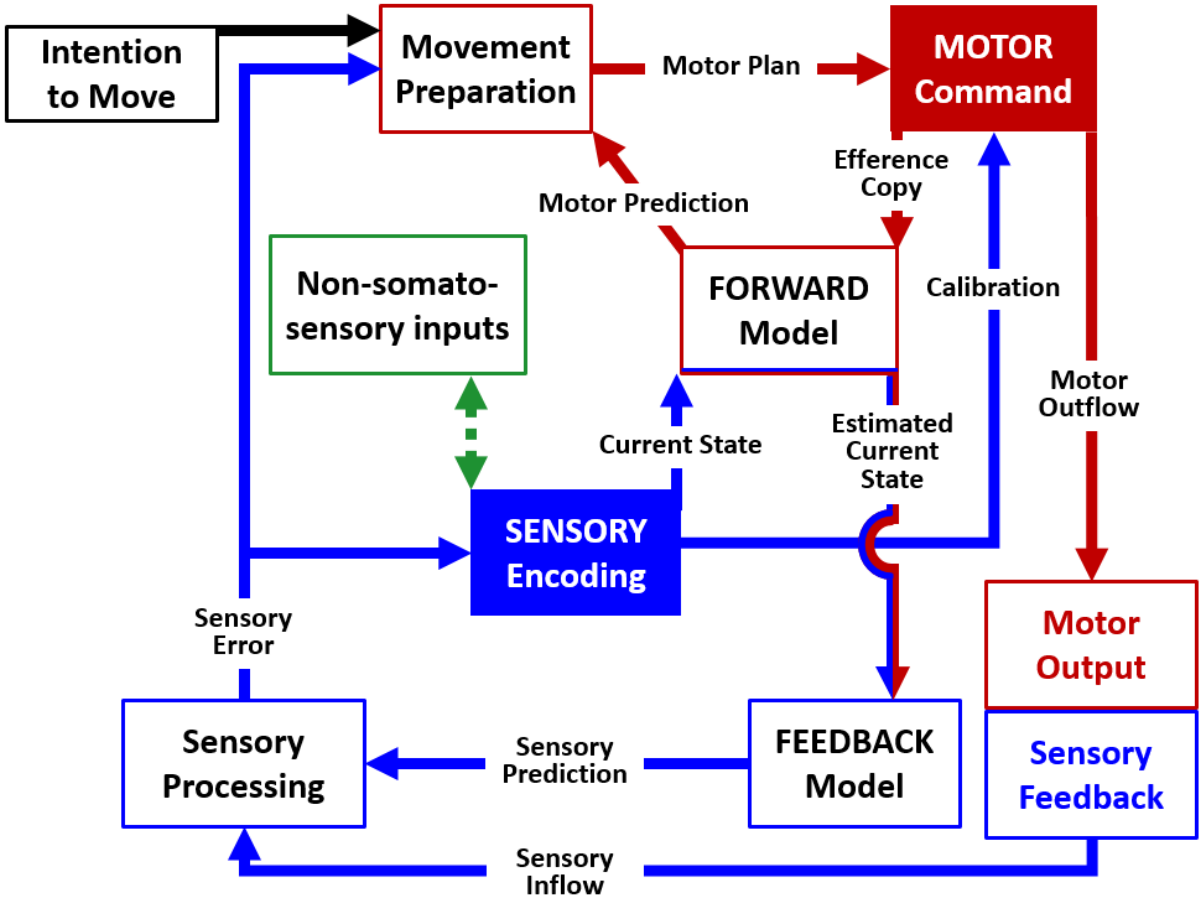

Figure 1: **Functional schematic representation of the SMILE model**. The signal sent by the motor command node (red arrow) comprises an efference copy processed by the forward model and a motor outflow generating a sensory feedback (blue arrows). Low-level nodes compare the actual sensory feedback to an anticipated sensory prediction generated by a feedback model and transmit information on the resulting sensory error to high-level nodes in order to calibrate the subsequent motor command. At the sensory encoding node, non-somatosensory inputs (such as vision or audition, green arrow and box) might be integrated to generate a more accurate representation of the current state.

translate them into motor commands (see Figure 1). This node generates the motor order and volleys the information to the periphery through the corticospinal tract. In parallel, an internal copy of this motor outflow (called efference copy, or corollary discharge) is integrated with the proprioceptive information ("current state") present in the high-level sensory encoding node. Potentially, non-somatosensory information (for example vision or audition) could also be integrated to enhance the precision of the current state estimation. Combining this current state with the efference copy allows a forward model to infer the final position of the body, even before the overt corresponding movement can be completed. Different hypotheses coexist upon the exact neural pathway followed by the efference copy, in particular on whether it transits through the sensory encoding node, or whether it is directly processed by the forward model (Borich et al., 2015). The

outcome of the forward model, carrying the expected post-movement proprioceptive state, is then volleyed to the motor planning node, which can therefore proceed to initiate the computations relative to the next required movement. The dual sensorimotor information emanating from the forward model node is also volleyed toward a feedback model which, based on the expected proprioceptive state, computes the sensory effects of the movement itself (sensory prediction). When the movement reaches its end, the difference between the anticipated sensory prediction and the actual sensory feedback is processed by low-level sensory nodes into a sensory error term. This is eventually fed back into the high-level preparation node, as well as the motor command node through the sensory encoding node, in order to calibrate the next movement. Through this multi-level feedback loop, the balance between the sensory and the motor processes is maintained.

2.2. Neuroanatomical SMILE

Based on the available data, we attempt to biologically situate the different nodes of the SMILE model. At the biological level, according to the SMILE model the movement preparation would be encoded by the premotor and supplementary motor regions (Ionta et al., 2010a). These regions would exchange information with M1, which would take the role of the motor command node (see Figure 2). M1 would then transmit the motor command toward the periphery, and simultaneously generates an efference copy volley to the parietal cortex, where it would be combined by the forward model (O'Reilly et al., 2013, Wolpert et al., 1998) with the proprioceptive current state emanating from S1. The feedback model encoded primarily by the cerebellum (Blakemore et al., 2000) would integrate the estimated current states to compute the sensory prediction. This latter would then be compared to the actual sensory feedback in the basal ganglia, thalamus, and cerebellum as low-level nodes. Then the signals processed by these low-level nodes would be sent to both the primary sensory encoding node (S1) and the premotor and supplementary motor area. The information sent by these three nodes (S1, premotor, supplementary motor area) toward M1, would then be used for the calibration of the subsequent motor output. The somatosensory feedback processed in coordination by the cerebellum, basal ganglia, and thalamus and then modulated by premotor, supplementary motor area, and S1, the motor execution commands are calibrated in M1, and the loop is complete.

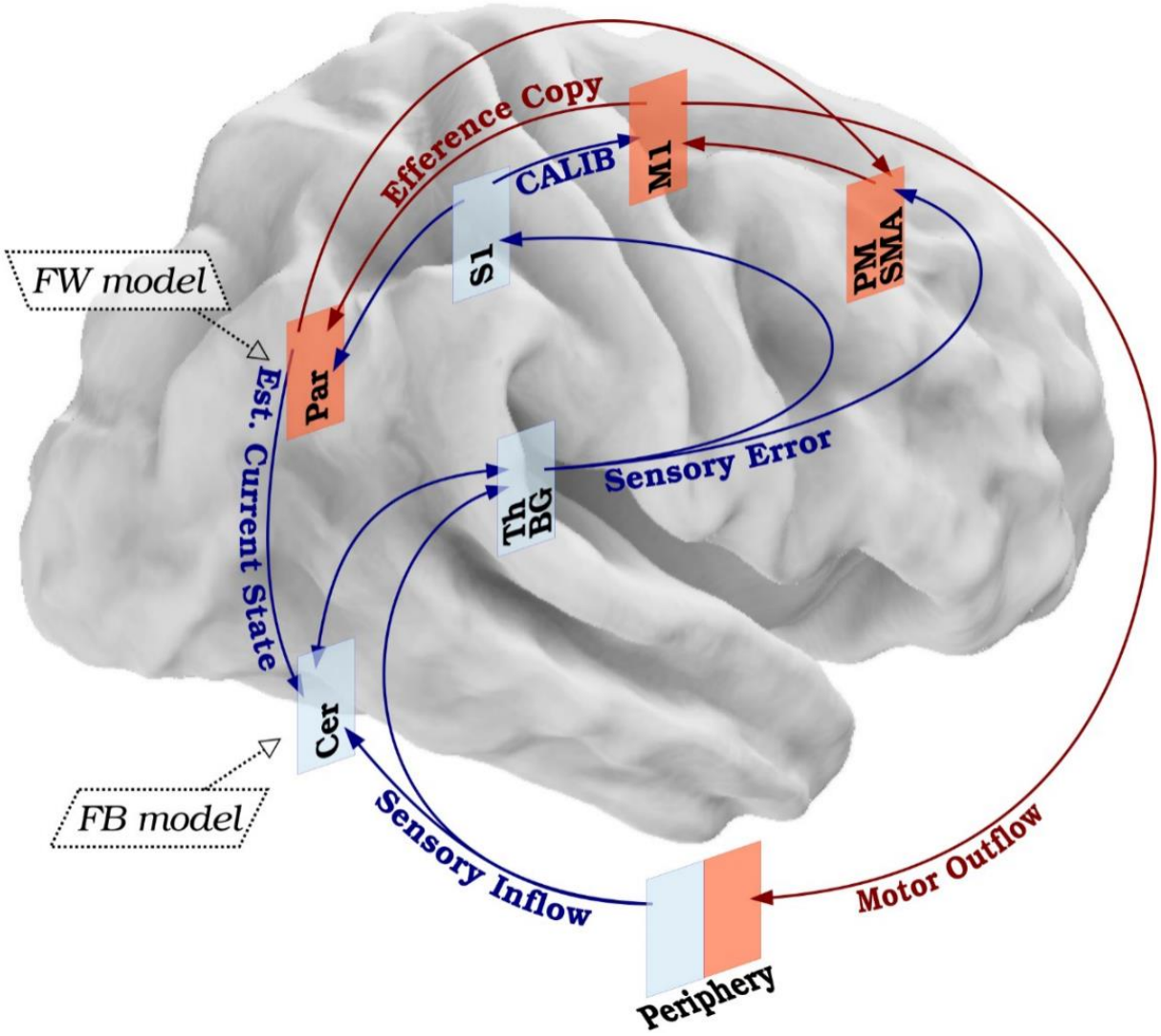

Figure 2: **Neuroanatomical configuration of the healthy SMILE model**. Healthy sensory-motor integration leads to balanced motor command and sensory feedback. The motor command (red arrows) from the primary motor cortex generates a sensory feedback (blue arrows), which is processed in low- and high-level modules and in turn calibrates the subsequent motor command itself.

S1	primary sensory cortex	BG	basal ganglia
PM	premotor cortex	Par	parietal cortex
Th	thalamus	CALIB	calibration
Cer	cerebellum	FW model	forward model
M1	primary motor cortex	FB model	feedback model
SMA	supplementary motor area	Est. Current State	estimated current state

3. Study A - Differential neural encoding of sensorimotor and visual body representations

Authors: David Perruchoud, Lars Michels*, Marco Piccirelli, Roger Gassert, Silvio Ionta.*
(contributed equally)*

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Contribution: The candidate performed the data analysis, and prepared the manuscript in collaboration with the Prof. Lars Michels, from the University Hospital of Zurich, Switzerland.

Based on the SMILE model, as a first step, we aimed at studying the relationship between changes in the sensory input and modifications in the movement preparation and associated nodes. To this aim we performed the following fMRI study, where we varied the features of the (visual) sensory input (presence or absence of a full-body attached to a hand) and verified the activation or inactivation of the sensorimotor network.

In a former study, we found that visual context affects the selection of different strategies during mental rotation (Ionta et al., 2012). In particular, if hand images are presented in isolation, participants rely on motor imagery, using an egocentric, first-person perspective. Conversely, if the hand images are presented attached to a full-body, the participants' response profile suggests the use of a visual imagery strategy, in an allocentric, third-person perspective. On this basis, we hypothesized that, at the neural level, the use of one or the other strategy (motor vs visual) would be reflected in the activation of different brain networks. Namely, mental rotation of hands should predominantly activate the sensorimotor network, which – according to the SMILE model – should include among others, pre-central, post-central, and parietal regions, as well as subcortical structures. Conversely, mental rotation of bodies (when hands are attached to a full-body) should primarily activate occipital regions.

To investigate this hypothesis, we adapted our behavioral experiment (Ionta et al., 2012) to the fMRI environment. We chose fMRI as the ideal neuroinvestigation technique because it provides access to deep structures, while the activation of subcortical areas via other conventional

neuroimaging technique, such as EEG, remains very challenging. We focused the data analysis on the direct contrast between “hands” and “bodies” because we wanted to uncover the differences between this two kinds of mental rotation, which in previous studies was only hypothesized on the basis of isolated contrasts (hands alone or bodies alone).

3.1. Abstract

Sensorimotor processing specifically impacts mental body representations. In particular, deteriorated somatosensory input (as after complete spinal cord injury) increases the relative weight of visual aspects of representations of body parts, leading to aberrancies in how images of body parts are mentally manipulated (mental rotation). This suggests that a sensorimotor or visual reference frame, respectively, can be relatively dominant in local (hands) versus global (full-body) bodily representations. On this basis, we hypothesized that the recruitment of a specific reference frame could be reflected in the activation of sensorimotor versus visual brain networks. To this aim, we directly compared the brain activity associated with mental rotation of hands versus full-bodies. Mental rotation of hands recruited more strongly the supplementary motor area, premotor cortex, and secondary somatosensory cortex. Conversely, mental rotation of full-bodies determined stronger activity in temporo-occipital regions, including the functionally-localized extrastriate body area. These results support that (1) sensorimotor and visual frames of reference are used to represent the body, (2) two distinct brain networks encode local or global bodily representations, and (3) the extrastriate body area is a multimodal region involved in body processing both at the perceptual and representational level.

4. Study B – Phase-locked modulation of M1 excitability during motor imagery.

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Contribution: The candidate developed the protocol and conducted the data recording, performed the data analysis and prepared the manuscript for a submission in a peer-reviewed journal.

Based on the SMILE model, we might expect that M1 (but also the parietal cortex) would be somehow activated during mental rotation, in particular of hands. In the fMRI experiment, we did not find such a pattern of brain activations. This could be explained by at least two reasons. First, we computed only the direct contrast between hands and bodies. Such a direct comparison could cancel out similar patterns of activity in the two conditions (hands, bodies), including e.g. M1 and the parietal cortex. Second, previous literature on the involvement of M1 in mental rotation is very controversial. Separate sets of studies respectively concluded on M1 being involved, or not involved, during mental rotation.

One possible reason for such inconsistence relates to the colossal inter- and intra-subject variability in the performance of the mental rotation task. To control this crucial methodological bias, and finally assert the involvement of M1 in mental rotation, we ran the following TMS study and designed a completely new methodological approach based on intra- and inter-subject normalization. With this approach we investigated the temporal dynamic of M1 activation during mental rotation of hands within the framework of the SMILE model.

The participants performed the mental rotation task on isolated hands, while TMS single-pulses were delivered to M1 in order to elicit motor-evoked potentials (MEPs) in the contralateral hand, at different time-points along the trial duration. In the light of M1 investigation, we chose TMS because it is a very specific and sensitive approach to probe the causal role of cortical activations, instead of the mere brain-behavioral correlational approach which characterizes both EEG and fMRI.

4.1. Introduction

The human brain is able to simulate perception or experience, in the absence of external stimuli. This concept is known as “mental imagery”, through which a cognitive process is internally generated without external inputs or outputs (Santo Di Nuovo et al., 2014, McNorgan, 2012). Even if the easiest example coming to mind would be visual imagery — for example when picturing a beautiful scenery experienced in the past — mental imagery can expand to a broad panel of modalities. Among others, “motor imagery” consists in the neural elaboration of a movement in absence of its actual motor execution (Kosslyn et al., 2001a). It can be explicitly elicited when imaging a given movement, but also implicitly, unconsciously performed in the framework of other cognitive processes. Such implicit motor imagery has been mostly investigated via the hand laterality judgement task, in which the participant is asked to determine the laterality of a hand visually presented in different views and orientations (Cooper and Shepard, 1975). This task has been shown to elicit implicit motor imagery via an unconscious mental rotation of one’s own hand into the position of the stimulus (Parsons, 2001, Parsons, 1987). Notably, response times (RTs) typically increase for biomechanically complex orientations of the stimuli (Parsons, 1994) or when the participants’ hands are constraint in an awkward posture (Ionta et al., 2012).

Like other modalities of mental imagery, motor imagery is bound by the concept of functional equivalence, according to which an imagined perception relies on similar neural substrates than the corresponding overt perception (Iacoboni et al., 1999, Jeannerod, 1995). Indeed, many neuroimaging studies have highlighted the involvement of several nodes of the sensorimotor network during motor imagery, such as the supplementary motor area, the premotor cortex, parietal areas, or the basal ganglia (Kosslyn et al., 1998, Kosslyn et al., 2001b, Perruchoud et al., 2016) Nevertheless, the involvement of the primary motor cortex (M1) during implicit motor imagery is still highly debated. Different neuroimaging studies have systematically reported M1 being activated (Kosslyn et al., 1998, Wraga et al., 2003, Lacourse et al., 2005, Hallett et al., 1994) or not (Kosslyn et al., 2001b, Parsons et al., 1995, Kuhtz-Buschbeck et al., 2003). Other studies suggest that M1 activity during mental rotation is only linked to the overt response related to a button press (Windischberger et al., 2003, de Lange et al., 2005, de Lange et al., 2008).

M1 activation in a given process can be specifically probed using transcranial magnetic stimulation (TMS), and several studies have attempted to resolve the argument thereby, again with contrasting outcomes. Two different approaches can be differentiated. Firstly, TMS can be used to disrupt a specific node in a hypothetical processing network; the observation of behavioral changes following the stimulation indicates the involvement of the target node in the investigated cognitive process. Alternatively, the amplitude of a motor evoked potential (MEPs) in the target muscle, is

indicative of the subjacent excitability of M1 at the time of stimulation. A modulation of this excitability suggests that M1 is involved in a specific process. Ganis et al. (2000) showed that TMS stimulation of M1 at 650 ms after stimulus onset results in an increase of RTs, and Tomasino et al. (2005) reached the same conclusion for a delay of only 400 ms. Both results suggest that M1 plays a crucial role in implicit motor imagery. But a deeper investigation by Sauner et al. (2006) using several time-points during the mental rotation of hands showed that M1 stimulation had no effect on task performance, regardless of the timing of the stimulation.

One possible reason for the discrepancy reported in those TMS studies emanates from their attempt to probe a single time-point of a process which presents a fundamentally high trial duration variation, from both intra- and inter-subject perspectives. For example, the seminal work from Parsons (1994) about mental rotations of hands reports RTs roughly in the range of 1500 ms. Contrastly, Tomasino et al. (2005) obtained mean RTs of about 950 ms . On the other extreme, Berneiser et al. (2016) reported mean RTs which could reach 2200 ms. Based on these evidences, the mean RT for such motor imagery can double between two participants, or even within a single subject, between different views or orientations of the same stimulus. To remedy to this issue, we therefore suggest a new paradigm approach, based on the TMS MEPs recording, whose pulse timing is determined as a function of the subject-specific and orientation-specific baseline response times. In this way, we were able to investigate the excitability of M1 at different phases of the mental rotation of hands, in a trial-normalized approach.

4.2. Methods

4.2.1. Participants

12 healthy and right-handed young male participants were enrolled in the experiment (mean age 23.2 ± 4.3 years; mean Edinburgh handedness score 92.5 ± 14.8). All participants had normal or corrected-to-normal vision and gave their written consent prior to the experiment. The experimental protocol was approved by the local Ethics Committee of the University of Verona (Italy), conducted at the Department of Neurosciences, Biomedicine and Movement Sciences (University of Verona), and was in accordance with the Declaration of Helsinki 1964.

4.2.2. Equipment

In each participant, we measured cortico-spinal excitability in all experimental conditions by means of motor-evoked potentials (MEPs) recorded at the level of the right hand. To record MEPs, three pairs of disposable bipolar electromyographic electrodes were positioned on the participant

right hand and forearm, in a belly-tendon montage, on the First Dorsal Interosseus muscle (FDI), the Abductor Digiti Minimi muscle (ADM), and the Flexor Digitorum Superficialis muscle (FDS). For each participant, the customized cortical motor hotspot was localized at the position of the TMS coil which elicited the maximal FDI excitation. The resting motor threshold was identified as the minimal stimulator output necessary to trigger five FDI MEPs of at least 50 µV out of ten trials. Any further stimulation was performed at 120% of the resting motor threshold. Focal TMS stimulation was carried out by a STM9000 Magnetic stimulator (ATES Medical Device, Italy) using a figure-of-height coil of 70 mm in diameter, producing a maximum output of 2T at the coil surface. Electromyographic signals were collected by a Digitimer D360 8-channel amplifier (Digitimer Ltd, Welwyn Garden City, UK) coupled with a CED Power 1401 coupled with Spike2 acquisition system (Cambridge Electronic Design Ltd, Cambridge, UK) to record and processed the data. Statistical analysis was performed using R (R Development Core Team, 2014).

4.2.3. Procedure and stimuli

The whole experiment was performed on a single day, in a timeframe of approximately 3 hours. The main task of the mental rotation was composed of short trials during which a realistic, colored photograph of a hand was presented on a screen 1m in front of the participant, on a visual angle between 6.5 and 8.5 degrees. All stimuli were normalized for luminance, and the paradigm was presented by E-Prime2 (Psychology Software Tools, Sharpsburg, USA). 16 different stimuli could be presented, following 3 factors, namely *Side* (left or right), View (palmar or dorsum), and *Rotation* (upright, medial, upside-down, and lateral, in 90° steps, see Figure 3).

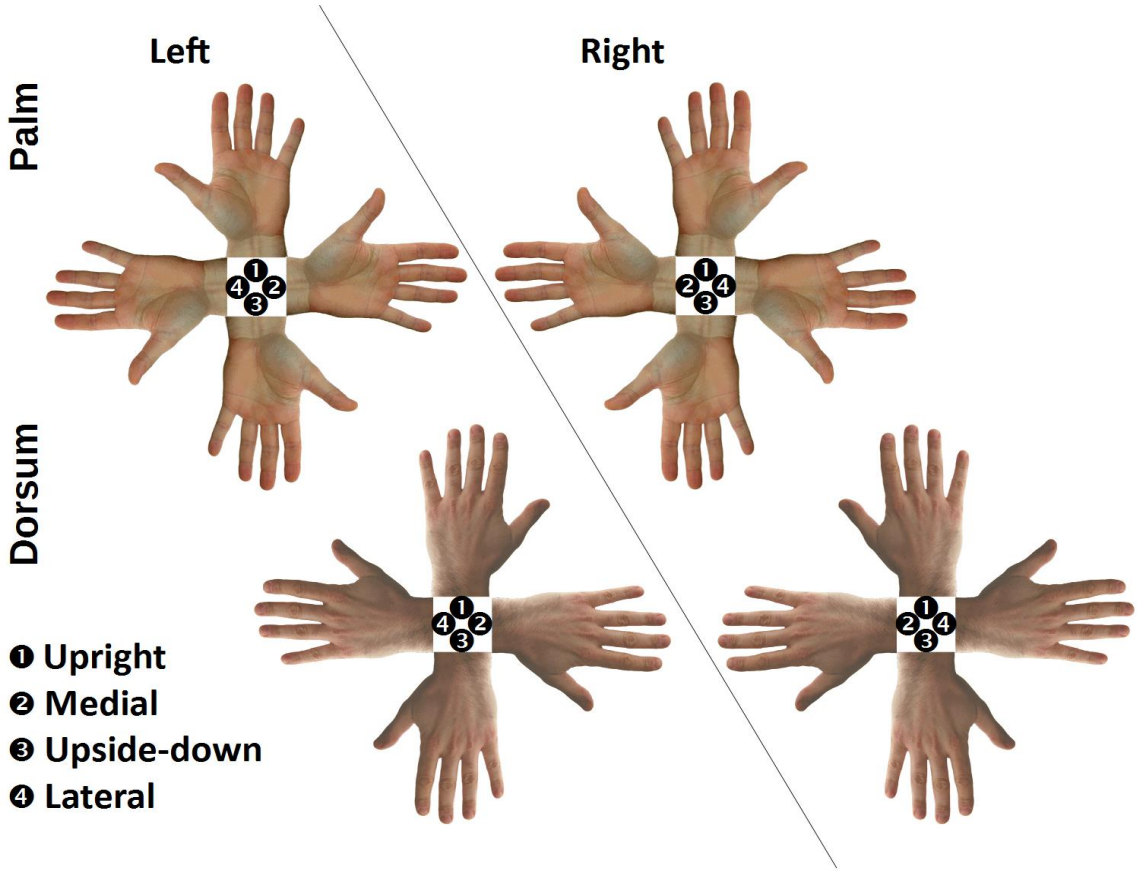


Figure 3 : **List of all visual stimuli.**

Participants sat comfortably in a chair, with their hands outside of their field of view, laying palm-down on their laps. Avoiding any unnecessary motor activity, they were asked to verbally report the laterality of the pictured hand, as fast and accurately as possible. The timing of their responses was recorded via a microphone, while the experimenter registered their accuracy. As soon as the participant had formulated an answer — or if the maximum trial duration of 3500 ms was reached without response — the stimulus disappeared, and was replaced by a grey fixation. The onsets of two successive trials were separated by 6 seconds.

The experiment started with a quick presentation of the study, and a training during which the participants could get acquainted with the task. To avoid conscious strategy selection, no mention of "imagery" was made during the explanation, letting the participants choose which strategy to adopt to solve the task. The training was intentionally long, with a maximum of 10 minutes, to ensure that the participants were comfortable with the task, and that they reached the plateau of their learning curve (i.e. stabilization of the RTs). During the training only, participants were given visual feedback

upon the accuracy of their responses. The baseline RTs was then evaluated, for each subject and each stimulus, by recording two blocks of 64 trials (total of 8 repetitions of each stimulus combination). These RTs were later used in the main task, to define the timing of the TMS pulses, as described below.

After a short session of 10 rest MEPs recording, the main experimental part was broken down into 6 blocks of 64 stimuli, each block lasting 6 minutes and 24 seconds. In these blocks, the TMS pulses could be given at 50%, 60% or 70% of the subject-specific baseline RTs for the corresponding stimulus combination. An extra set of trials did not involve any TMS pulse. Three of the participants had extra pulses given at 30% and 40% of their baseline RTs, resulting in blocks of 9 minutes and 36 seconds. Between two blocks, participants were allowed a break of approximately 5 minutes. After the 6 blocks, 10 more rest MEPs were recorded, and the experiment ended with the revised Edinburgh Inventory to score the handedness of each participant (Oldfield, 1971, Dragovic, 2004).

4.2.4. Analysis

Trials were discarded if the answer given by the participant was wrong, or if the participant failed to give an answer within the maximal duration of 3500 ms. Following previous studies, trials whose RTs were shorter than 500 ms were discarded as well (Ionta and Blanke, 2009, Ionta et al., 2012). Finally, unexpected loud noises in the vicinity of the experiment could prematurely trigger the microphone, and such trials were discarded as well. Altogether, 8% of the trials were discarded. For the remaining valid trials, the MEP amplitudes in the three target muscles were divided by the participant-specific mean rest MEPs recorded before and after the main experiment, to express the MEP amplitudes as a percentage of rest MEPs. To solve the issue of the high variability of the RTs, the timing of each TMS pulse was expressed as a percentage of the current trial duration. For example, if the TMS pulse was given at 700 ms after stimulus onset, and the RT for the trial was 1150 ms, this pulse would have a trial-percentage of 61% (see two examples on Figure 4**Erreur ! Source du renvoi introuvable.**). This way, the timing of TMS pulse was normalized both across participants and across stimuli. For the analysis, all trials falling into a percentage-bin of 15% were pooled together. Because the number of TMS pulses delivered under 40% of the trial duration were not sufficient, the analysis consisted of 4 percentage-bins (40%-55%, 55%-70%, 70%-85%, and 85%-100%). In the example above, a trial-percentage of 61% would result in the corresponding trial being pooled in the bin of 55%-70%. Three different MEPs analyses were carried out, each comparing two precise features of the stimuli. (1) The *postural awkwardness* factor of the trial was broken into familiar (upright and

medial rotations) and awkward (upside-down and lateral rotations), based on earlier behavioral studies (Parsons, 1987). The other two analyses consisted of (2) the *side* factor (left- and right-hand stimuli) and (3) the *view* factor (palm- and dorsum-hand stimuli). In each case, the mean MEP ratio for a given factor and percentage-bin was estimated for all 12 subjects, and both distributions were then compared via a paired t-test, with FDR multiple comparison across percentage-bins. This allowed for the investigation of the M1 excitability with respect to specific features of the stimuli. Any effect was considered significant for $P_{FDR}<0.05$.

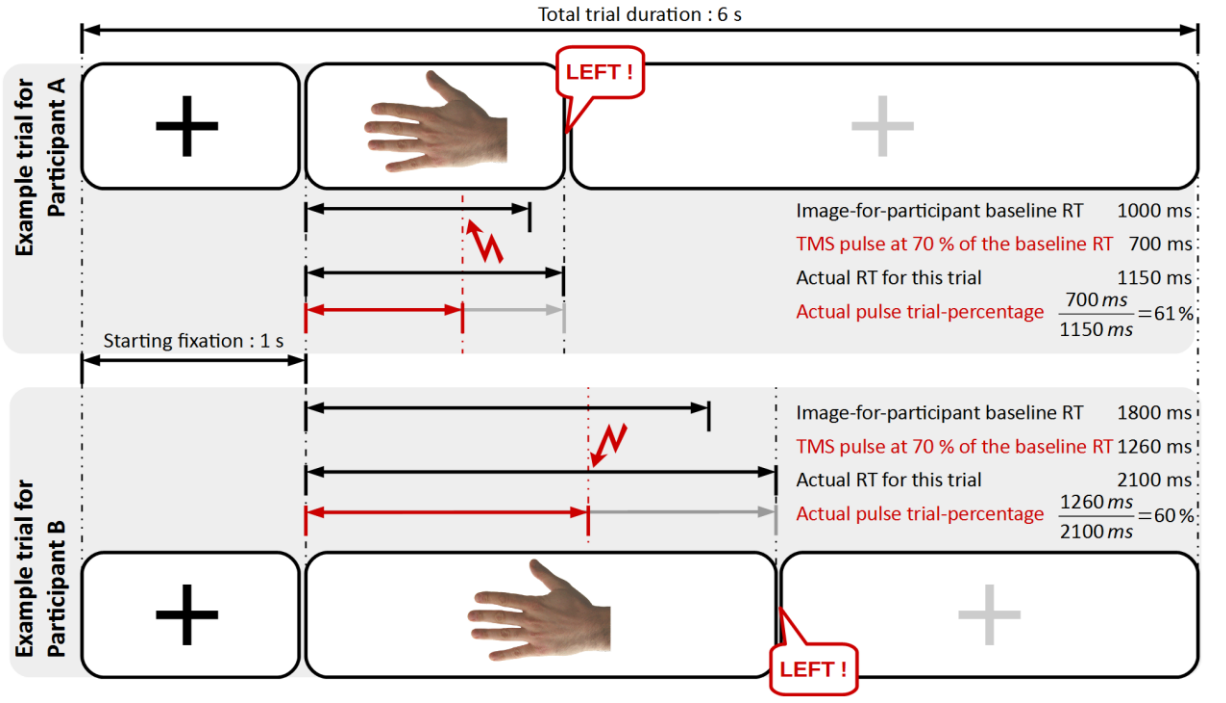


Figure 4 : **Trial schematic, with examples of timing calculation for a trial in two different participants.** The top panel presents a response-time of 1150 ms and a TMS pulse given at 700 ms post-stimulus (i.e. 70% of the subject- and stimulus-specific baseline of 1000 ms). Because of the TMS pulse timing and the actual trial RT, these values results in a trial-percentage of 61% of the normalized trial duration. Therefore, this trial would be pooled in the 55%-70% percentage-bin for later analysis. The bottom panel depicts a hypothetical trial for another subject, with the same stimulus, and following the same calculations. Notice how both trials would be pooled in the 55%-70% percentage-bin, despite emanating from different RT and TMS timings.

4.3. Results

4.3.1. Behavioral results

The accuracy of the participants' responses was adequate (mean accuracy 92.9%, SD=4.9%, range from 81.5% to 98.2%). The three-way ANOVA on the RTs with the factors of *Side* (2 levels, left and right), *View* (2 levels, palm and dorsum) and *Rotation* (4 levels, upright, medial, upside-down and lateral), computed on the valid trials without TMS pulse, showed a main effect of *Side* ($F(1,11)=5.62$, $p=0.02$), with shorter RTs for the dominant (right) hand, as well as the main effect of *Rotation* ($F(3,33)=12.04$, $p<0.001$). The two-way interaction of *View* x *Rotation* also showed significance ($F(3,33)=4.94$, $p=0.003$, see Figure 5). The presence of the medial-over-lateral-advantage (Funk and Brugger, 2008), in which laterally-presented hands are mentally rotated slower than medially-presented ones – particularly on the palm-view rotations – suggests that our participants' performance was indeed modulated by biomechanical constraints, and hence it is likely they relied on motor simulation strategies to solve the task. Any other main effect, two-way, or three-way interactions, appeared to be not significant (all $p>0.54$). The inter- and intra-subject variabilities of RTs are presented in the Figure 6. Importantly, the timing of the TMS pulse (50%, 60% or 70% of the baseline RTs) did not lead to any significant changes in the participants' RTs, as revealed by a one-way ANOVA ($F(3,45)=0.05$, $p=0.99$, not shown here).

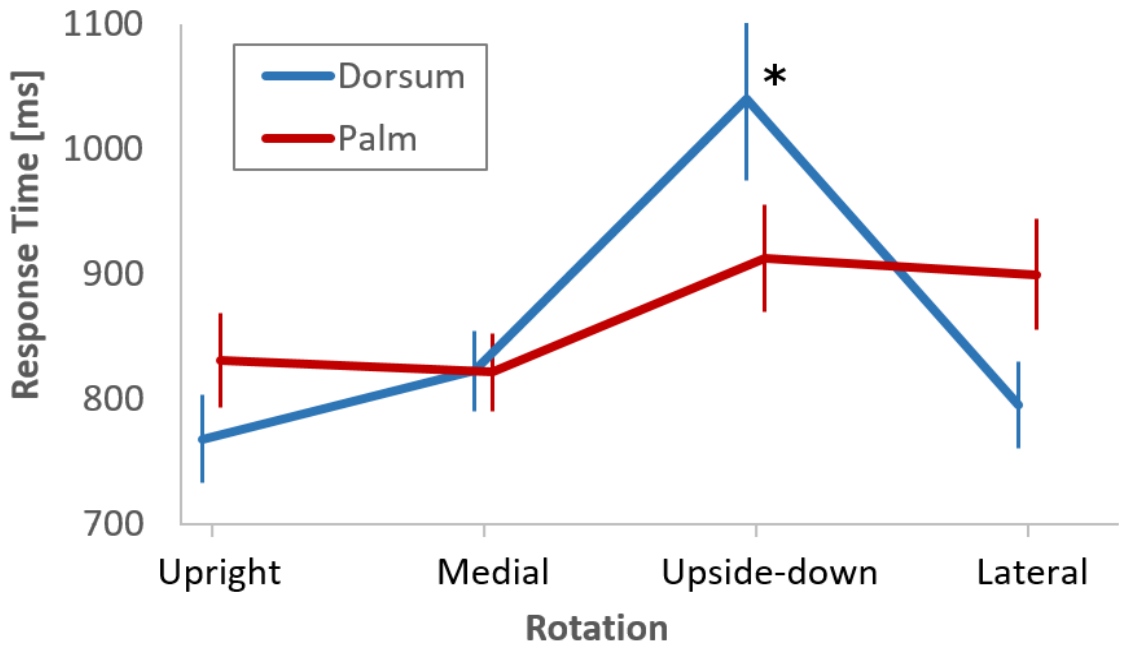


Figure 5 : **Response times without TMS stimulation.** The "medial-over-lateral" effect on the palm views indicates the use of a motor strategy to solve the task. The error bars denote standard error of the mean. * denotes p(Tukey)<0.05 to all other data points.

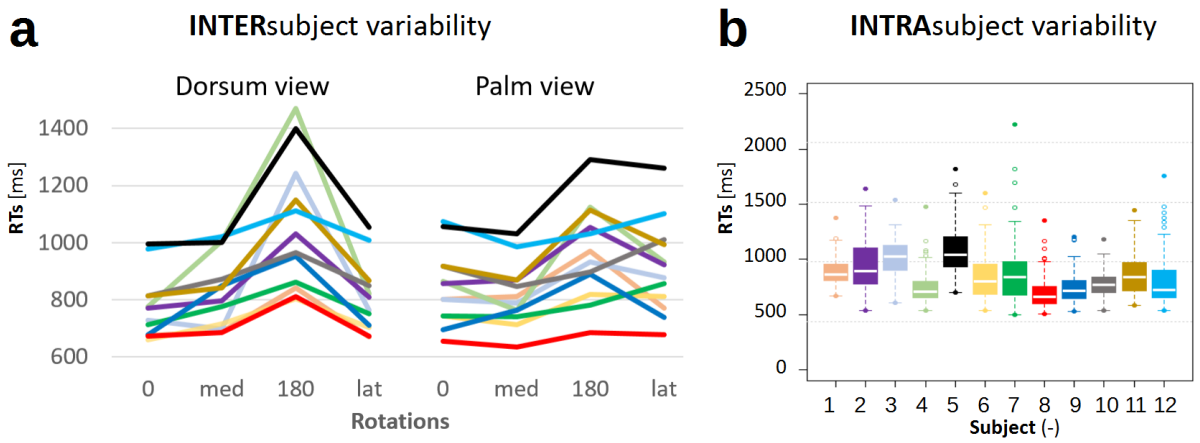


Figure 6 : **Inter- and Intra-subject variability. (a)** Mean response times for view and rotation, for each of the 12 participants, in the valid trials without TMS pulses. Each color represents a different participant. Notice the wide intersubject variability, for example between participant 5 (in black) and participant 8 (in red). **(b)** Distribution of all valid trials (pooled across both views and all orientations) without TMS pulse, for each subject. The full dots represent the fastest and slowest trials of each participant. Color code corresponds to A. Notice that within subject, the duration of different trials can for example span between 500 and 2200 ms (participant 7, in dark green).

4.3.2. M1 excitability results

When comparing the postural awkwardness factor (i.e. upright and medial hand rotations for *familiar*, and upside-down and lateral rotations for *awkward*), the 55%-70% percentage-bin shows statistically significant differences for both FDI (P=0.0329) and ADM (P=0.0153) (see Figure 7, top), with the *awkward* condition resulting in both cases into an increase of the cortical excitability. When comparing the two possible stimulus views (see Figure 7, bottom), only the FDS muscle shows a significant difference in the 70%-85% percentage-bin (P=0.0188), with palm view resulting in an increase of the cortical excitability. Finally, when comparing the laterality of the stimuli, M1 excitability did not present any significant difference between the left and right stimuli, regardless of the target muscle (see Figure 7, middle).

4.4. Discussion

In this study, we investigated the modulation of corticospinal excitability of M1 during the mental rotation of hands. A cohort of previous studies investigating similar processes have fail to reach a consensus, on neither the laterality (de Lange et al., 2008, Thayer and Johnson, 2006), temporal dynamics (Ganis et al., 2000, Tomasino et al., 2005), nor even on such broad matter as the

involvement of M1 during motor imagery (Kosslyn et al., 1998, Kosslyn et al., 2001a, Hallett et al., 1994).

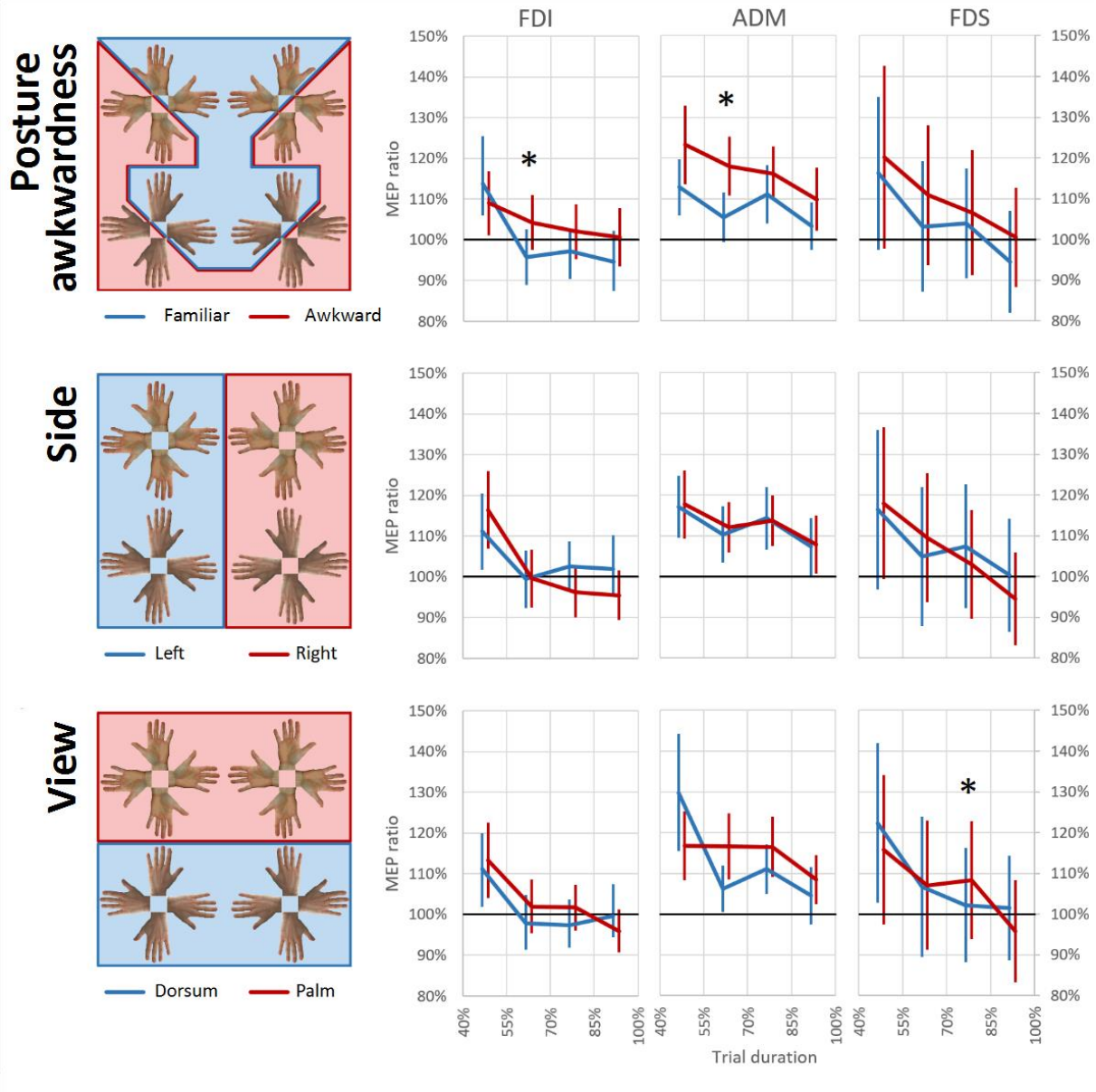


Figure 7: **Phase-locked M1 excitability during mental rotation of hands.** Results are given at different percentage-bins of the trial performance, probed via MEP amplitude. The task MEP amplitudes in the three hand and wrist muscles are compared to the mean rest MEP recorded before and after the paradigm (100%). The statistical significance is computed by paired T-tests between two types of stimuli, within a single percentage-bin. The top panel presents the comparison between biomechanically familiar (upright and medial rotations) and awkward (upside-down and lateral rotations) movements. The middle panel presents the comparison between left and right stimuli. The bottom panel presents the comparison between the dorsum and palm view of the stimuli.
* denotes PFDR<0.05. Error bars denote the standard error of the mean.
FDI : First Dorsal Interosseus ; ADM : Abductor Digiti Minimi ; FDS : Flexor Digitorum Superficialis

4.4.1. The flawed approach of stimulus-locked analysis

We suggest that such inconsistencies might emerge from the prevailing but potentially flawed approach of stimulus-locked analysis, to investigate a process exhibiting widely varying intra- and inter-subject trials durations. Here, we propose a novel methodological approach normalizing these specific variations by establishing the timing of the process in post-processing, based on the single-trial duration instead of the customary stimulus-locked or response-locked approaches. Using this novel methodology, we were able to evidence specific time-windows in terms of trial duration percentages, during which the corticospinal excitability of M1 was differentially modulated by particular stimulus features.

The existent evidences on TMS studies of M1 during mental rotations of hands have relied on these potentially flawed stimulus-locked or response-locked approaches, and have reached diverging outcomes. Tomasino and colleagues (2005), showed that single-pulse TMS on the hand area of left M1 lengthened the RTs of a same/different pair-matching task of hands rotations, when the pulse was delivered 400 ms after the stimulus onset. These results are in direct contradiction with an earlier study, in which Ganis et al. (2000) highlighted – in a very similar approach – a behavioral effect of TMS with a 650 ms delay post stimulus onset, but critically not at 400 ms, for both hands and feet mental rotations. This discrepancy could originate from disregarding the different performances in term of trial duration. Indeed, the mean RTs reported in those two studies show a trend consistent with their outcomes, with the mean RTs approximating 925 ms, respectively 985 ms for Tomasino et al., respectively Ganis et al., results. Additionally, the pair-matching task, in which a pair of rotated hands has to be identified as either same, or mirror images of each other presents an inherent limitation. As suggested by Zacks et al. (2008), the strategy adopted by the participants to solve such a task can have critical outcomes on the results, as it could engage either motor or visuospatial imagery.

Building on this discrepancy, Sauner et al. (2006) delivered single-pulse TMS to the left M1 at 6 different post-stimulus time-points (0-1000 ms, in steps of 200 ms) of an actual hand laterality judgement task while recording MEPs, thus addressing several of the limitations previously stated. None of their stimulus-locked time-points revealed any effect on performance nor cortical excitability during the mental rotation of hands. Nevertheless, their small cohort, and the complexity of their multi-factorial analysis, could have masked some potential effects. In particular, RTs for left hand rotations around the upside-down direction show a clear increase for stimulations at 400 ms compared to the trials where the TMS pulse was delivered immediately with the stimulus onset, but

this effect goes unnoticed and unreported in their four-way ANOVA analysis. Their design also allowed them to investigate the response-locked behavior of MEPs in the last 400 ms before toe-press, here again, only showing a lateralization effect, that they interpret as a secondary effect of the task. Furthermore, based on the difference of the mean RTs between their fastest and slowest orientations, Sauner et al. suggested that the motor rotations phase of the mental rotation of hands should last a minimum of 150 ms. Applying the same principle to our data, the motor rotation phase would be lasting at least 30% of our normalized trial, on average. Our selected 15% bin-size is therefore expected to allow the identification of any potential effect of interest.

A final study from Pelgrims et al. (2011) claimed that the previously reported discrepancies could be originating from the somatosensory feedback inherent to suprathreshold TMS stimulation, interfering with the motor process. To address this concern, they stimulated left or right M1 between 100 and 500 ms after stimulus onset with 10 Hz subthreshold repetitive TMS (train of 5 pulses) during mental rotation of hands. They showed that this TMS stimulation impairs the RTs for hands, but not letter rotations, irrespective of the stimulus laterality. This inconsistency with the results presented by Sauner et al. could arise from three scenarios. (1) RTs might not be sensitive enough to detect the ephemeral disruptive effect of single-pulse TMS on M1. (2) Single-pulse TMS might be insufficiently potent to carry an actual disruptive effect on M1, as opposed to the rTMS protocol presented in the Pelgrims. Finally, (3) the large interventional window (400 ms of rTMS, plus after-effect) might indirectly adjust for the potential poor phase-locking of the TMS stimulation in the single-pulse case. By interfering with the target node thorough a longer virtual lesion effect, a potentially short critical time-window might be stimulated more consistently across trials than by the single-pulse approach.

Our approach examined this third possibility and aimed to address the aforementioned limitations of the previous studies while investigating the cortical excitability of M1 along the partitioned duration of normalized trials. In our novel paradigm, the timing of the TMS pulse was defined in term of percentage of the total trial duration, on a trial-by-trial basis, instead of relying on the usual stimulus-locked or response-locked approaches. With this approach, we were able to highlight both general and muscle-specific modulations of the cortical excitability of M1 in distinct normalized time-windows along the trial durations.

4.4.2. Posture awkwardness related activation

In particular, while performing hand mental rotations toward biomechanically awkward postures (upside-down and lateral orientations), MEPs amplitude was significantly higher than for

biomechanically familiar postures (upright and medial orientations), during a time-window of 55% to 70% of the full-trial duration (see Figure 7, top panel). This effect is similar to the so-called "medial-over-lateral" effect (Funk and Brugger, 2008), built on the specific anatomical exertion during lateral versus medial rotations.

We interpret this modulation of the corticospinal excitability of M1 as a generalized activation of the M1 neural counterparts corresponding to the hand muscles during the actual processing of the motor imagery. The executed movement toward complex terminal positions involves a global strain in the hand muscles, but not a specific wrist pronation nor supination, reason why this activation is only occurring in the hand muscles, but not in FDS. The timing of this activation is also consistent with the current model of the sequential phases of the mental rotation of hands, as the stimulus has first to be visually interpreted and requires an initial guess of hand laterality before the motor imagery phase takes place (Parsons, 1994, Thayer and Johnson, 2006). The last portion of the total trial duration has to be devoted to the response processing, by mapping the handedness judgement to the corresponding motor response, vocal in our case. The exact timing of this process has not yet been precisely defined, but previous results estimate the response-specific processing of the hand laterality judgement task to the last 80-120 ms (Kawamichi et al., 1998), when the response is given by pressing a button. The mean RTs reported for this task by different studies seem to not drastically differ whether the response modality was carried out by button pressing, toe switch, or verbal response. Based on these premises, with the global mean RTs of 890 ms, the response-specific mental processes of our experiment would on average befall into the last 9-13% of a trial, which corresponds grossly to our choice of bin size. In other words, the last percentage bin of our analysis (85% to 100%) is likely to mostly incorporate the response-specific processing, during which the outcome of the mental rotation is mapped to the correct verbal answer, and generates the vocalization.

Critically, and unlike the previously reported effect of single-pulse TMS during mental rotations of hands (Ganis et al., 2000, Tomasino et al., 2005, Pelgrims et al., 2011), this effect on the biomechanical constraints of the motor imagery shows a direct relationship between the amplitude of the effect, and the angle of the stimulus. Because our analysis on biomechanical posture awkwardness is directly computing paired comparisons between 2 sets of 2 different rotations (upright and medial versus upside-down and lateral), any statistically significant effect would show a differential effect of the angle of stimulus. We suggest that this difference with previous literature is based on the increased sensitivity of our approach, based on normalized trial duration, with respect to the classical stimulus-locked approaches used in the previous studies. Potentially, the detection of our effect could also emerge from a higher sensitivity of MEPs to the motor imagery processes,

compared to the dependent variable used in many of the earlier studies, namely RTs (Ganis et al., 2000, Tomasino et al., 2005, Sauner et al., 2006). Indeed, MEPs recordings represent a direct monitoring of the M1 cortical activation, potentially linked to motor imagery, while RTs are the outcome of a long process combining several sequential phases.

4.4.3. Absence of Laterality-related modulation

In the present study, we only delivered TMS stimulation to the left M1, as it has been consistently showed that the left motor and premotor areas are likely involved not only in the motor processes of the contralateral limbs (and hands in particular), but also of the ipsilateral counterpart during motor imagery or observation (de Lange et al., 2008). Meanwhile, and especially for motor imagery, the right M1 seems to only affect the contralateral limbs. Nevertheless, this strict lateralization of the motor process is still under debate, as many studies emphasized a broader role of right M1 (Pelgrims et al., 2011). In particular, some believe that both right and left M1 can serve sequential, but essentially different phases of executed reaching movement, irrespective of the laterality of the effector limb (Schaefer et al., 2007, Sainburg, 2002). An alternative hypothesis in the context of mental hand rotations, is that each M1 considers the matching between the mental rotation outcome and the biomechanical constraint of its contralateral hand (Johnson, 1998, Parsons, 1994, Papadelis et al., 2007). Our data show that the left M1 activation is not differentially modulated by motor imagery of left or right hands (see Figure 7, middle panel). Combined with the general activation reported above, which suggest a potential role of M1 in motor imagery, this absence of laterality effect is in line with the current hypothesis that the left M1 is equally involved in both hands motor imagery, irrespective of the laterality of the target limb. Because of the high hemispheric specialization of motor imagery reported in earlier studies, any claim on the right M1 is impossible with our design, and would require to repeat the experiment with right M1 TMS stimulation. Also, the verbal response required by the participants could theoretically bias the results of laterality, as it is well-known that speech production is almost exclusively processed in the left hemisphere. But such an influence on our paradigm is unlikely, since vocal response is expected to be counterbalance in all of our comparisons.

4.4.4. Muscle-specific activation

Our data also show coherent muscle specificity in corticospinal excitability. When comparing the two different views of the stimuli. Processing palmar views of the hand resulted in an increase of

MEPs amplitude in the FDS muscle compared to dorsal views, within the 70% to 85% bin of trial duration. As participants performed the experiment with their hands on their knees, with palm down, the palm view trials required an additional imagined supination of the wrist, to rotate the imaged palm toward the viewer. FDS has been previously shown to be activated during execution of the wrist supination (Pizzolato et al., 2012). The timing of this activation in our experiment places it downstream from the activation reported in the posture awkwardness case. This would suggest a specific sequence of the imagined movements required to solve the task, with the wrist rotation occurring later than the initial activation.

4.5. Conclusion

Altogether, our data identified a characteristic increase of M1 excitability at a specific time-window during the motor imagery process. This time-window occurs very late in the whole process, as the main activity modulations are detected between 55% and 85% of the whole trial duration. Even though it would contradict the very purpose of this study, we can translate these percentages back into pure post-stimuli timings, in order to compare with previously reported results. With the global mean RT of our experiment of 890 ms, this gives an approximate target window for motor processes in mental rotation of 500 ms to 750 ms after stimulus onset. This is consistent with many studies who identified M1 or general motor activations on the late processing of mental rotations of hands. Besides the study from Ganis et al. (2000) reported above, Lebon et al. (2012) identified an interaction of rIPL with M1 during mental rotations of hands, via an elegant dual-pulse experiment given at 650 ms after stimulus onset. In a magnetoencephalographic recording, de Lange et al. (2008) identified a motoric suppression of alpha and beta waves starting approximately 300 ms after stimulus onset, and lasting until the end of each trial. Finally, Thayer and Johnson (2006) showed that electroencephalographic modulations of evoked-related potentials were present during the same task within a broad window of 600 to 1200 ms after stimulus onset, and were stronger during a window of 700 to 1000 ms. All of these results are consistent with the original model for mental rotation of hands developed by Parsons (1994), in which the motor imagery is preceded by an earlier necessary visual phase, as well as an initial “educated guess”, taking the shape of an implicit perceptual analysis (de Lange et al., 2008).

In summary, using the novel methodology proposed here, we could identify the specific time-window, on a trial-specific approach, during which motor processes are involved in mental rotation of hands and are represented by a modulation of the excitability of M1. This highlights the critical importance of considering inter- and intra-subject behavioral variability when investigating the

temporal dynamics of the motor processes during the hand laterality judgement task in future studies.

5. Clinical application 1: the case of dystonia

Dystonia is a disabling movement disorder characterized by muscle contractions and frequently associated with abnormal movements and/or postures (Fahn et al., 1998). It is the third most common movement disorder after essential tremor and Parkinson's disease (Breakefield et al., 2008). It affects movement execution either at a global or local level. On the basis of this topographical distinction, dystonia can be defined as general or focal. Focal hand dystonia (FHD) is one of the most common forms of focal primary dystonic disorders (Tarsy and Simon, 2006, Jankovic, 2009). Despite steadily growing clinical experience, little is known about its etiopathogenesis, and our understanding of its pathophysiology is still insufficient (Zoons et al., 2011). For these reasons the treatment is limited to only symptomatic therapy, such as focal application of botulinum toxin (Hallett et al., 2009). The development of novel treatment strategies for FHD is limited due to this lack of in-depth knowledge about the underlying pathophysiological mechanisms. This is where the SMILE model can be applied. Accommodating the main three pathophysiological mechanisms of FHD (loss of inhibition (Hallett, 2011), aberrant neural plasticity (Quartarone and Pisani, 2011), and defective learning-based sensorimotor integration (Byl, 2007)), the SMILE model proposes a plausible source of FHD and can be extended to other sensorimotor impairments.

5.1. Sensory-Motor deficits in Focal Dystonia

5.1.1. Behavioral Data

Behavioral data can be used to generate hypotheses regarding candidate nodes and/or links within putative models that contribute to disorder-related alterations, as well as to individuate specific impairments (and therefore improve the understanding of the pathology) and also to assess early markers of a given disorder even before the first manifestation of the clinical symptoms (Scontrini et al., 2009). In the case of dystonia, two main behavioral tasks have been largely used: the Spatial Discrimination Threshold (SDT) and the Temporal Discrimination Threshold (TDT).

5.1.2. Spatial characteristics of dystonic disorders

The SDT task establishes the minimal distance between two stimuli that participants can reliably discern as distinct events. Healthy subjects can detect changes in the orientation of tiny parallel grooves as thin as 1 mm when presented on the tip of the finger (Craig and Kisner, 1998). The SDT has

been largely used in populations suffering from a variety of dystonic disorders. For example, varying the thickness and intervals of the grooves allows to reliably investigate disorder-related sensory features (Van Boven and Johnson, 1994).

Starting from the hypothesis that dystonias are associated with an aberrant organization of the sensory cortex, Bara-Jimenez et al. (2000) compared the abilities of blindfolded FHD patients and healthy controls in localizing tactile stimuli delivered either to a single phalanx or to each individual phalanx of the right (dystonic) hand. Spatial sensitivity was impaired in dystonic patients only when stimuli were delivered to different regions on the same phalanx.

Bara-Jimenez et al. (200b) likewise presented FHD patients with "Johnson–Van Boven–Philips" domes and observed an impaired ability in FHD patients to discriminate grating orientation. Sanger et al. (2001) replicated these results and additionally showed that SDT was also impaired in the non-dominant, non-symptomatic hand. On this basis, it could be suggested that the disorganization due to FHD is not limited to a single body part but rather extends to the whole body (or at least to the contralateral hand).

To explore whether the impairments in SDT tasks are specific for FHD or are also detectable in other types of dystonias, Molloy et al. (2003) conducted an experiment with domes applied bilaterally on the tip of the index fingers of a broad panel of dystonic patients, including general dystonia, FHD, blepharospasm, and cervical dystonia. Their findings contrast with the unspecific SDT impairment reported by Sanger et al. (2001). General dystonia patients displayed similar performance compared to healthy subjects, while all focal dystonia patients showed impaired SDT. Importantly, only FHD patients showed a significant threshold difference between dominant and non-dominant hands. Therefore, it still needs to be clarified whether the spatial discrimination impairments observed in FHD patients are restricted to only the symptomatic limb or are instead bilateral.

5.1.3. Temporal characteristics of dystonic disorders

Another frequently used task in dystonia-related research is the TDT, which identifies the minimal time interval between two stimuli that allows differentiating them as separate events. It typically involves unimodal electrical stimulation of the skin, but can be coupled, paralleled, or even replaced by visual, kinematic, or any other type of stimuli. On average, healthy subjects can discriminate two electrical stimuli on the index finger provided they are separated by at least 30 ms (Lacruz et al., 1991).

In dystonic patients there is evidence of abnormalities not only in spatial discrimination, but also

in temporal processing. In an investigation of a heterogeneous set of dystonic patients (5 generalized, 1 focal hand, and 1 upper-body segmental dystonia), a single or pair of non-noxious tactile stimuli were applied to both index fingers with various inter-stimulus intervals. In comparison with healthy controls, dystonic patients exhibited an increased TDT (Tinazzi et al., 1999). In a subsequent study, Tinazzi et al. (2002) showed that in FHD the temporal threshold drastically increases with the distance between the stimulation sites. Since these outcomes could theoretically result from a general integration issue, Aglioti et al. (2003) extended the paradigm to visual-tactile stimulation in an investigation restricted to generalized dystonia patients. Using either electrical tactile stimulation of the index finger and/or visual stimuli with LEDs, they revealed increased TDT compared to healthy controls in all conditions, though particularly marked in the cross-modal situation. Additionally, they showed that temporal order judgments (i.e. the explicit reporting of the temporal order of several asynchronous stimuli) are also impaired in generalized dystonia patients (Aglioti et al., 2003). When conducting a similar experiment in FHD patients, the TDT for unimodal visual stimuli resulted in similar performance between patients and controls (Fiorio et al., 2003).

These collective data suggest a critical difference in the mechanisms of FHD and generalized dystonia. FHD patients' impairment appears to be linked to tactile processing and visual-tactile integration, whereas the generalized dystonia patients exhibit more general impairments in integration processing, including exclusively visual processing of stimuli near the hands. This interpretation has been further confirmed in cervical dystonia (Tinazzi et al., 2004) and blepharospasm (Fiorio et al., 2008); two other types of focal dystonia which yielded similar results. By comparing performance with corresponding non-dystonic patients (i.e. cervical pain and hemifacial spasms, respectively), it has been shown that the impairment is selective for dystonic disorders (Tinazzi et al., 2004, Fiorio et al., 2008).

Temporal discrimination seems to be affected both at symptomatic and non-symptomic body surfaces. Scontrini et al (2009) stimulated either the hand, neck, or eyebrow in 82 focal dystonia patients including blepharospasm, FHD, cervical, and laryngeal dystonia. They observed a general increase of the discrimination threshold for all the investigated body parts (Scontrini et al., 2009). This corresponds with the spatial studies reviewed above, as well as with a study in which abnormalities in TDT during uni- and multi-modal visual-tactile processing were shown to be linked to the non-fully penetrant gene in both manifesting and non-manifesting carriers (Fiorio et al., 2007a).

Overall, most studies present a coherent picture of the relationship between dystonia and temporal discrimination threshold, whose increase in focal dystonia is specifically selective for somatosensory processing, but not isolated to the symptomatic limb, while generalized dystonia can be attributed to a more general integration deficit.

5.1.4. Kinesthetic impairments in dystonia

It has been demonstrated that the so-called “vibration-induced illusionary movement” (the illusion of movement induced by tonic vibration of a tendon) is impaired in dystonic patients compared to healthy controls (Tempel and Perlmutter, 1990). In order to assess the properties of this illusion in focal dystonia, Grünewald et al. (1997) recruited patients suffering from cervical dystonia, FHD, and healthy controls. All participants were blindfolded and were asked to mimic the movements of one arm with the other arm. The “master” arm was either moved passively by the experimenter, or illusionary “moved” by means of vibration-induced illusionary movement with 50 Hz tonic vibrations at the level of the biceps tendon. As expected, dystonia patients could accurately track passive movements. However and unlike healthy subjects, tracking during illusory conditions was bilaterally impaired, even if the vibration-induced flexion was normal (Grunewald et al., 1997). This suggests an impairment of the kinesthetic pathway, while the perception of position would remain intact (see also Rome and Grunewald, 1999; Yoneda et al., 2000; Frima et al., 2003).

5.2. Structural Imaging

Few studies investigated the structural brain organization of FHD and the available data are largely inconsistent. Some studies associated FHD with anatomical abnormalities at the cortical level (Delmaire et al., 2007, Garraux et al., 2004), some others to sub-cortical abnormalities (Granert et al., 2011b, Draganski and Bhatia, 2010). In particular, part of the evidence from structural brain imaging on in the pathophysiology of dystonia highlights the role of abnormalities in subcortical structures, including the basal ganglia (Krystkowiak et al., 1998, Bhatia and Marsden, 1994, Beukers et al., 2011, Draganski et al., 2009), mesencephalon (Vidailhet et al., 1999), and the cerebellum-thalamus-cortex axis (Argyelan et al., 2009). Conversely, other studied associated FHD with structural abnormalities at the cortical level, including the sensorimotor (Garraux et al., 2004, Delmaire et al., 2007) and the premotor cortex (Granert et al., 2011a).

The directionality of volumetric differences between FHD patients and controls does not provide a straightforward means of individuating a precise neural substrate responsible for, or at least associated with the symptoms (see Table 1).

Region	Increased volume	Decreased volume
Prefrontal Cortex	Egger et al., 2007	Draganski et al., 2003
Inferior Parietal Lobe	Etgen et al., 2006	Egger et al., 2007
Cerebellum	Draganski et al., 2003	Delmaire et al., 2007
Thalamus	Obermann et al., 2007	Delmaire et al., 2007
Putamen	Bradley et al., 2009	Obermann et al., 2007

Table 1: **Dystonia-related volumetric changes.** Previous studies have reported conflicting results in cortical, basal ganglia and cerebellar regions.

5.3. Functional Imaging

In several neuroimaging studies on active movements in FHD, patients were asked to physically perform the movement while functional magnetic resonance imaging (fMRI) data were recorded. In order to test the hypothesis that a dysfunctional balance between neighboring finger representations could be one origin of FHD, a recent study required FHD patients to control a cursor on a screen by regulating the force applied on one or two mouse buttons with their affected hand (Moore et al., 2012). With respect to healthy controls, FHD patients showed decreased activity in bilateral S1, right parietal cortex and cerebellum, and left putamen, during the coupled movement.

If only coupled movements are specifically affected by FHD, it might be hypothesized that the pattern of cerebral activity would vary as a function of movement difficulty. Accordingly, FHD patients have been asked to use the affected hand to either write (complex movement) or flex/extend the fingers while fMRI data were recorded (Havrankova et al., 2012). Consistent with Moore et al. (2012), Havrankova et al. showed the hypoactivation of S1 and parietal cortex. However, no involvement of cerebellum or basal ganglia was reported. Additional investigations on the potential influence of movement complexity showed premotor hyperactivity and cerebellar hypoactivity associated with unimanual and bimanual finger tapping in FHD patients with respect to controls (Kadota et al., 2010). Hu et al. (2006) asked FHD patients to perform progressively more complex kinds of writing while being in the fMRI scanner and, with respect to healthy controls, they found increased activation in motor cortex, basal ganglia and cerebellum associated with complex writing (using the pen) but no differences for simple writing (using the finger). This would support the view that movement complexity plays a central role in the symptoms exhibition and the relative cerebral activity; however, the involved network does not match other data.

Despite such initial agreement, the level of inconsistency between different studies addressing similar issue increases as slightly different tasks are performed by FHD patients. Abnormal neural activity has been reported in basal ganglia (Peller et al., 2006, Schneider et al., 2010, Blood et al., 2004, Chase et al., 1988, Siebner et al., 2003), thalamus (Preibisch et al., 2001, Hu et al., 2006), sensorimotor cortex (Preibisch et al., 2001, Islam et al., 2009, Jankowski et al., 2013), and supplementary motor areas (Hu et al., 2006, Oga et al., 2002). Such inconsistencies in the literature are best exemplified by controversial findings regarding the discordant level of activity reported in prefrontal (Preibisch et al., 2001, Dresel et al., 2006, Pujol et al., 2000, Playford et al., 1998) and primary motor areas (Detante et al., 2004, Dresel et al., 2006, Playford et al., 1998, Pujol et al., 2000, Ceballos-Baumann et al., 1995, Ibanez et al., 1999).

However, the functional neuroimaging studies that investigated the features of sensorimotor representations in FHD – by asking patients to physically perform a movement – might be affected by a methodological issue which could dramatically undermine their validity. Indeed, there is strong evidence supporting that the sensory feedback during movement execution is altered in FHD.

One possible way to overcome this limitation is to investigate the pattern of neural activity at rest. The comparison of the correlation between activity changes in different brain areas during different tasks and rest brought to the scientific community one of the most robust findings throughout the last years of neuroimaging science: the implication of the medial prefrontal cortex, temporo-parietal junction, and precuneus in a canonical network dubbed as the 'default mode network' (e.g. Buckner et al., 2008) (Gultepe and He, 2013). Investigating the properties of the default mode network in FHD patients by analyzing the changes in resting-state networks, Mohammadi et al. (2012) found that FHD patients show reduced patterns in postcentral regions and augmented patterns in basal ganglia. These data speak in favor of disorganization at the level of the sensorimotor system, in particular the basal ganglia and the somatosensory cortex; both important for coding the afferent sensory feedback. However, despite the undisputed advances brought by the resting-state approach in circumventing potential confounds due to altered sensory feedback, it still does not provide information on the origin of task-specificity, one of the most peculiar aspects of FHD (see 1.3 Motor imagery to dissociate sensory and motor mechanisms).

Considering the hypothesized mechanisms of FHD and the possible structure described in the SMILE model, we further propose that FHD is the manifestation of a breakdown in the sensory-motor loop as the result of a disorganization targeting S1 and due to over-training-related abnormal neuroplasticity, impaired cortico-subcortical dynamics and local loss of inhibition. Based on evidence

showing that FHD patients exhibit impairments in temporal and spatial discrimination, but not in overt motor behaviors other than the task-specific ones, one first hypothesis is that the breakdown of the sensory-motor integration happens in the high-level nodes, specifically in S1. The breakdown would determine no equivalence between the signal sent from the periphery to S1, and the signal sent from S1 to M1 (calibration). When M1 sends the signal to the periphery through the brainstem, the peripheral muscle activation (through the cerebellum, basal ganglia, and thalamus) sends a feedback signal to premotor, supplementary motor and primary sensory regions, which in turn have back projections to equivalent areas in M1. We hypothesize that if the gain of the signals sent through this loop is superior to 1, then M1 keeps increasing its firing until maximal muscle contraction occurs, that is the typical cramp of FHD (see Figure 8A).

Taking into account the possibility that the deterioration of the sensory information could happen in the low-level nodes and that the whole thalamus-basal ganglia circuit preserves somatotopic organization all along (Vitek 2002), a second hypothesis is that S1 receives already "disordered" sensory errors from the sub-cortical and cerebellar modules. This would imply that only a fraction of the sensory feedback could be impaired, i.e. the component for the hand, supporting that sub-cortical modules, and thus the feedback from cerebellum-thalamus-basal ganglia complex to S1 (plus the signal from S1 to M1) is impaired and causes problems downstream (see Figure 8B).

The SMILE model explains (1) task-specific impairments in terms of a breakdown in only some sub-components of the sensorimotor loop, (2) increasing muscle contraction resulting in cramps as a function of the unbalance between sensory input and motor output, and (3) spreading activity to agonist muscles (due to overlapping cortical representations) as a function of extremely repetitive behaviors that would cause cortical disorganization. Taking into consideration this tight association between sensory input and motor output, it is clear how crucial their dissociation is for better understanding the nature of their integration, and therefore the implementation of mental rotation as investigation tool in future experimental protocols.

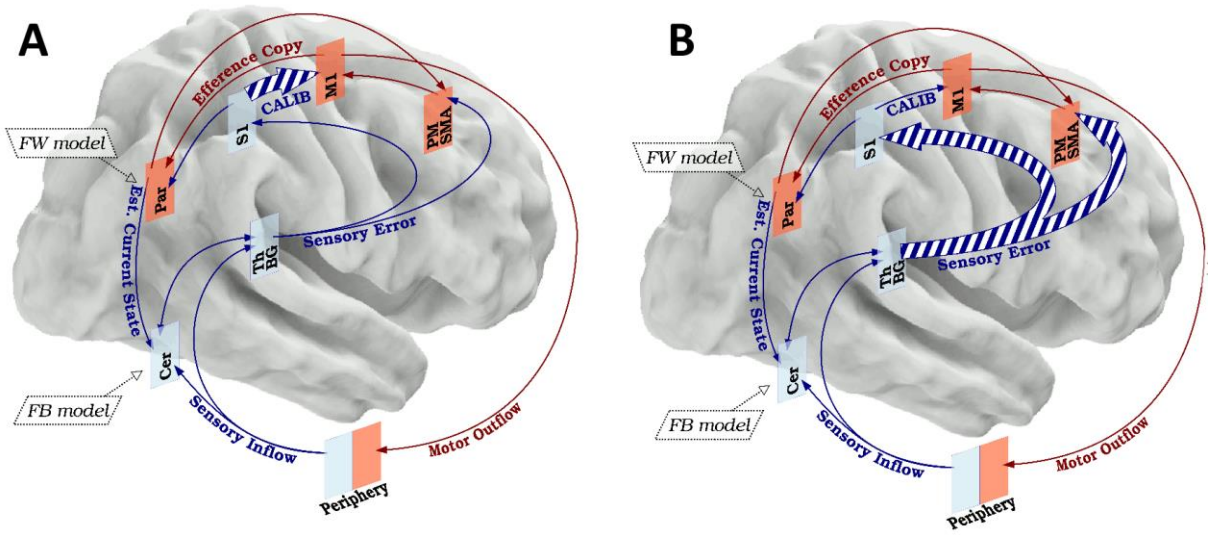


Figure 8: **Disorganization of the SMILE model in FHD. A)** According to a first hypothetical disorganization, in FHD the sensory feedback is altered between S1 and M1, resulting in an abnormal motor command. **B)** A second hypothesis concerns the possibility that the sensory information is distorted already in the low-level nodes, resulting in an altered signal transmitted from the sensory processing nodes to S1 and the movement preparation nodes (PM-SMA).

The dashed arrows represent qualitative anomalies in signal processing. The size of the arrows represents the quantitative features of the signal. Red, respectively blue boxes and arrows depict motor-, respectively sensory-related nodes and connections.

S1	primary sensory cortex	BG	basal ganglia
PM	premotor cortex	Par	parietal cortex
Th	thalamus	CALIB	calibration
Cer	cerebellum	FW model	forward model
M1	primary motor cortex	FB model	feedback model
SMA	supplementary motor area	Est. Current State	estimated current state

5.4. Potential Mechanisms of FHD

5.4.1. Loss of Inhibition

For several decades, the excitatory/inhibitory regulations of the central nervous system have been proposed as impaired in both general dystonia and FHD (Tinazzi et al., 2009). Atypical excitability and activity would result in the deterioration of the communication pathways between the central nervous system and the periphery. Nevertheless, testing this type of hypothesis is particularly challenging using conventional neuroimaging or behavioral techniques, due to the difficulty of distinguishing between excitatory or inhibitory processes. In order to overcome this

limitation, Transcranial Magnetic Stimulation (TMS) – a non-invasive technique allowing the excitation or inhibition of specific brain regions through magnetic pulses – has been largely used to study the properties of given cortico-spinal pathways (Miniussi and Thut, 2010). The features of the "motor-evoked potentials" (time-locked electromyographic activity resulting from a supra-threshold TMS pulse over the motor cortex) and Cortical Silent Period (CSPs; the interval of silent electromyographic activity following a supra-threshold TMS pulse) can provide information regarding the underlying state of the neural populations. In healthy subjects, the typical duration of CSPs for TMS stimuli of 120% of the motor threshold is about 70 ms (Saisanen et al., 2008). In FHD the (a)typical CSPs are shortened (Kimberley et al., 2009), restricted to the symptomatic hand (Chen et al., 1997), and task-specific (Tinazzi et al., 2005b). For example, Tinazzi et al. (2005a) used CSP together with a facilitation/rest electromyographic motor-evoked potentials to demonstrate the task-specific motor impairment of FHD. In this study, while TMS was delivered and motor-evoked potentials were recorded, participants performed both pincer grip (a finely tuned activations of an isolated subset of muscles of the thumb and index finger) and power grip (a co-contraction of all digits). With respect to healthy controls, FHD patients had different CSPs and motor-evoked potentials depending on the type of grip performed. In particular, while pincer grip elicited shorter CSPs and larger motor-evoked potentials amplitude ratio, power grip remained unchanged, supporting the specificity of excitatory/inhibitory impairment mechanisms in FHD (see also Kimberley et al., 2009).

In addition to CSP, other types of inhibition features are potent markers of neural pathway mechanisms, and have been shown to present abnormalities in all types of dystonia at the level of both the central and the peripheral nervous system (Hallett, 2006, Lin and Hallett, 2009). At the central level, intracortical surround inhibition (the capacity of an excited neuron to reduce the activity of the neighbors) is decreased in FHD (Lin and Hallett, 2009, Espay et al., 2006, Ridding et al., 1995, Chen et al., 1997). At the peripheral level, reciprocal inhibition (the coordinated contraction and relaxation of agonist and antagonist muscles, respectively) is dramatically impaired in FHD patients (Nakashima et al., 1989, Panizza et al., 1990).

Animal studies showed that aberrant intracortical surround inhibition can lead to dystonic behaviors (Matsumura et al., 1991, Matsumura et al., 1992). In humans such loss of inhibition can be investigated using TMS (Hallett, 2007). For example, Sohn et al. (2004) set the TMS pulses as stimulating the portion of the primary motor cortex (M1) corresponding to the little finger, but triggered by the activity elicited by self-initiated flexion of the index finger. Using this approach, the authors investigated surround inhibition in FHD patients by evaluating the little finger reactivity

during volitional flexion of the index finger. Their results showed that in FHD patients the motor-evoked potentials' amplitude was increased.

In addition to intracortical surround inhibition, also interhemispheric inhibition (the ability of a unilateral hemispheric stimulation of the motor cortex to inhibit the contralateral motor cortex given a short latency) is impaired in FHD (Sohn and Hallett, 2004, Beck et al., 2009). Interhemispheric inhibition is usually investigated with dual-site TMS, where a conditioning stimulus is applied in one hemisphere, and shortly followed by a test stimulus in the corresponding sensorimotor area of the contralateral hemisphere. In healthy controls the conditioning stimulus has a suppression effect over the test stimulus (Perez and Cohen, 2009). Analyzing the amplitude of motor-evoked potentials of this test-pulse allows the investigation of the underlying modulation of interhemispheric inhibition. Beck et al. (2009) showed that interhemispheric inhibition is partially lost in patients with mirror dystonia, while non-mirror dystonia patients exhibited similar performance compared with healthy subjects. This discovery suggests that interhemispheric inhibition is not deeply involved in the basic pathophysiology of dystonia, but only in its mirror aspect. In order to investigate the task-specificity of inter-hemispheric inhibition in mirror dystonia, Sattler et al. (2013) extended the previous study with a rest versus pen-holding task. At rest, the inter-hemispheric inhibition levels of all three groups (healthy subject, mirror and non-mirror FHD) were similar, but mirror patients displayed a large bilateral decrease in inter-hemispheric inhibition in the pen-holding condition, inversely related to the severity and duration of symptoms. Altogether, these two studies agree on the involvement of impaired inter-hemispheric inhibition in mirror dystonia, but this latter is not directly involved in the pathophysiology of focal dystonia itself, since it does not occur in non-mirror dystonia situations.

Some groups focused on psychogenic dystonia, a type of dystonic disorder without a clear neurological basis and possibly associated with other psychological disorders. In this vein, Espay et al. (2006) used TMS for investigating a broad range of behavioral features in both psychogenic and organic (non-psychogenic) dystonia. These features included reciprocal inhibition, CSPs, but also cutaneous silent period, as well as short- and long-intracortical inhibition. All of these behavioral markers were statistically different between healthy subjects and dystonia patients. The only statistically relevant difference between behavioral results in psychogenic and organic dystonia involved reciprocal inhibition.

Altogether these data suggest that different types of dystonia, whether primary or secondary to psychological disorders, share basic mechanisms as well as widespread cortical and subcortical abnormalities. The neurological mechanisms underlying these behavioral outcomes might not be the original cause for dystonia, but simply the consequence of upstream unknown dysregulation. Nonetheless, numerous studies have linked dystonia symptoms with the abnormal synchronous

activity of numerous modules in the basal ganglia-thalamocortical circuit (Vitek 2002). While synchronous neural activity is involved in the planning and execution of movement in healthy subjects, dysregulation in the degree of synchronization might disrupt the proper function of the sensorimotor feedback system a whole (Schnitzler and Gross, 2005).

5.4.2. Abnormal Neural Plasticity

Neural plasticity refers to the ability of the brain to adapt its neural connections to the requirements of the environment as a result of learning. Animal studies showed that over-trained repetitive movements abnormally remodels somatosensory cortical maps, leading to sensory de-differentiation between the receptive fields of neighboring digits (Byl, 2007). This de-differentiation parallels the development of dystonic-like behaviors (Byl et al., 1996, Blake et al., 2002). In other words, after a prolonged and intense stimulation, the neuron which previously coded the sensory input relative to only one finger starts to respond to sensory inputs delivered to more fingers (Byl et al., 1997). Indeed, dystonia-related changes of receptive field features have been reported in sub-cortical structures such as the pallidum and thalamus (Lenz et al. 1998), key nodes in the generation of sensory and/or motor representations. Such neuro-plastic changes would be at the basis of aberrant pairing of tactile stimuli in healthy subjects (Godde et al., 1996), or excessive repetitive movement patterns in FHD patients (Altenmuller and Jabusch, 2010, Roze et al., 2009). Experimental evidence showed that FHD is associated with such de-differentiation in areas S1 and S2 (Butterworth et al., 2003), basal ganglia (Quartarone et al., 2008, Rothwell and Huang, 2003), and cerebellum (Thompson and Steinmetz, 2009). Interestingly, non-manifesting carriers of a gene supposed to be involved in developing dystonia exhibit impairments in sequence learning but not in motor learning (Ghilardi et al., 2003). This supports the proposition that dystonia is a complex disorder due to aberrant integration mechanisms, biologically based on abnormal neuronal plasticity and dynamics, as a predisposing endophenotypic trait (Quartarone and Pisani, 2011).

In a recently developed methodology called “paired-associative stimulation”, sensory stimuli are paired with TMS cortical stimulation depending on the basic level of cortical plasticity. Thanks to this method, it is possible to create an artificial and relatively long-term association between an event and the TMS pulse. Using median nerve stimulation and TMS over S1 to elicit paired-associative stimulation, Tamura et al. (2009) showed that in healthy subjects paired-associative stimulation intervention had no notable effects on any measure of cortical excitability or inhibition. Conversely, in FHD patients, the waveform elicited by TMS increased right after paired-associative stimulation, suggesting an abnormally increased excitability of S1.

In a recent extension of this study, and following the emerging hypothesis according to which cerebellar dysfunction might be tightly linked to the development of focal dystonia (Raike et al., 2012), Hubsch et al. (2013) used theta-burst stimulation of the cerebellum to investigate how its excitability can influence cortical plasticity of M1 in FHD. Theta-burst stimulation is a repetitive TMS protocol in which short trains of 3 high-frequency magnetic pulses are repetitively discharged to a brain area. It is used to modulate the short-term excitability level of a given brain area. In that prospect, Hubsch et al. (2013) used theta-burst stimulation on cerebellum followed by paired-associative stimulation of M1 and showed a complete loss of cerebellar influence on sensorimotor plasticity, specifically for FHD patients. In the same study, the authors also showed that FHD patients had both lower performances in learning a new task and in "washing out" a previously learned task in order to adapt to a modification. These data suggest that the loss of cerebellar influence on sensorimotor cortex might be linked to atypical plasticity of the sensorimotor cortex.

5.4.3. Defective Learning-based Sensory-Motor Integration

According to the defective sensorimotor learning hypothesis, the different types of dystonia would be characterized by functional alterations in the sensorimotor circuit supposed to integrate sensory input and motor output (Breakefield et al., 2008). In this view the dystonic behavior would be due to abnormal somatosensory feedback received by the motor system during the movement. Accordingly, it has been shown that over-practice can cause an overlap of the somatosensory receptive fields (Butterworth et al., 2003), which would lead to altered sensory representations and therefore to abnormal motor behaviors. In favor of this hypothesis, there is evidence that finger representations in FHD patients are spatially closer (Bara-Jimenez et al., 1998), providing the biological justification to the notion that FHD develops in conjunction with excessive sensory stimulation or over-repetition of motor tasks (Quartarone et al., 2006).

The aberrant sensory input would be due to the disorganization of S1(Hinkley et al., 2009). The overlap of digit representations in S1 would lead to excessive gain in the sensorimotor loop, due to the incongruence between the somatosensory and motor maps (Sanger and Merzenich, 2000). This incongruence would lead to a saturation of motor commands resulting in the dystonic movement of the affected hand or even in the muscular over-contraction and consequent paralysis. In this way the altered sensory representations would lead to abnormal motor behavior, highlighting the importance of sensorimotor integration. The critical role of the sensory feedback in modulating motor responses

(Abbruzzese and Berardelli, 2003) is demonstrated by evidence showing how sensory discrimination is impaired in patients suffering from writer's cramp (Sanger et al., 2001) as well as by the altered sensorimotor integration mechanisms in patients presenting musician's dystonia (Rosenkranz et al., 2000) and writer's cramp (Murase et al., 2000). In addition to experimental data, the importance of sensory processing in an apparently purely motor disorder such as FHD, is also demonstrated by the effectiveness of sensory re-training procedures (Zeuner et al., 2002). Despite short-term duration and reversibility, FHD patients can significantly improve their spatial acuity by performing daily sessions of Braille reading sessions for 8 weeks (Zeuner and Hallett, 2003).

However, the nature of the relationship between disorganized somatosensory information and aberrant motor output is still under debate. One possible explanation is that long-lasting non-physiologic motor behavior can cause changes in somatosensory representations. Alternatively, abnormal somatosensory representations may lead to abnormal motor output explaining the particular dystonic phenotype. Consequently, one of the main focuses for future research will be to investigate movement mechanisms in FHD and other types of movement disorders, but ruling out any confounding effect due to abnormal sensory feedback.

5.5. Mental Imagery and Rotation to investigate Sensorimotor mechanisms

To identify the origin of dystonic behaviors it is crucial to understand the features of sensorimotor integration mechanisms while avoiding any potential confound due to altered sensory feedback. One possibility to achieve this goal is to use an investigation tool that does not require movement execution. This would help differentiate the mechanisms related to altered sensory feedback from those related to abnormal sensorimotor representations. Mental imagery is a cognitive task with such characteristics. In healthy subjects, physical execution and mental imagery of a movement –"motor imagery"- share similar temporal and kinematic properties (Sirigu et al., 1996). The association between the properties of executed and imagined movements is further demonstrated by clinical studies showing how physical impairments are reflected in mental imagery. For example, if patients suffering from hemi-Parkinson's disease are asked to physically perform and mentally imagine specific manual movements with the affected and the unaffected hand, the response times of the imagery task will be proportional to the asymmetries in the physical task; that is longer latencies for the affected than the unaffected hand (Dominey et al., 1995). Some data described the effects of FHD on motor imagery of different movements. In particular, in order to understand whether the physical impairments due to FHD generally or specifically influence the characteristics of mental imagery, patients suffering from writer's cramp were asked to physically

perform and mentally imagine finger tapping and writing (Tumas and Sakamoto, 2009). Surprisingly, with respect to healthy controls patients had longer motor imagery latencies for both actions, suggesting that FHD would lead to unspecific deficits in mental imagery of complex movements.

In healthy controls, physical movement and motor imagery also engage partially overlapping brain networks (Grezes and Decety, 2001). In particular, physical practice modulates the imagery-related brain activity in a specific network including the supplementary motor area, basal ganglia, and cerebellum (Ionta et al., 2010a). Several data support that also in clinical populations there is an association between the performance in motor imagery and the quantity or quality of neural activity. For example if Parkinson's disease patients are asked to physically perform and mentally imagine hand and wrist movements, they show longer latencies and decreased activation patterns in fronto-parietal regions (Samuel et al., 2001). In addition, if Parkinson's patients with freezing of gait perform motor imagery of walking, with respect to healthy controls their response times are longer and brain activity is decreased in the supplementary motor area and increased in the mesencephalic locomotor region (Snijders et al., 2011).

Through the manipulation of cortico-spinal excitability by means of TMS, motor imagery can be used to investigate not only the properties of cortical representations but also the characteristics of the communication between the central nervous system and the periphery. In particular, in healthy subjects top-down imagery-related mechanisms regulate the excitability of the sensorimotor pathways (Fourkas et al., 2006), and in Parkinson's patients the typical cortico-spinal excitability in response to the imagination of a movement is drastically reduced with respect to healthy controls (Tremblay et al., 2008). With regard to FHD patients, Quartarone et al. (2005) delivered the TMS pulse while participants were imagining index flexion. Similarly to the results shown by Sohn and Hallet (2004) on movement execution, during motor imagery the amplitude of motor-evoked potentials of all recorded hand and forearm surround muscles was increased in FHD patients, even for the arm not involved in motor imagery (Quartarone et al., 2005). This highlights the broad and less focused muscular activity in FHD patients compared with healthy subjects, even in the case of simple imagined movements.

In order to deepen the investigation on motor imagery and to evaluate the impact of motor imagery on motor excitability in dystonia, another group conducted an experiment on patients suffering from flaccid leg paresis due to psychogenic dystonia (Liepert et al., 2011). In this study, single and double TMS pulses were delivered while patients imagined ankle flexion. The amplitude of motor-evoked potentials resulting from the TMS pulse over the foot/leg motor cortex decreased with respect to rest, while it increased in healthy subjects (Liepert et al., 2011). This finding suggests an amplification of motor-imagery-related cortical excitability. Interestingly, during ankle movement

observation on a video, motor-evoked potentials modulation of both healthy controls and psychogenic dystonia patients were similar (Liepert et al., 2011). Altogether with the motor imagery results, these data emphasize the difference between self-referred motor mechanisms and other-oriented visually based processing in focal dystonia.

Only few brain imaging studies investigated the neural circuits recruited by motor imagery and their task-dependent activity in FHD. In one of the first studies addressing this issue, post-stroke secondary FHD patients were asked to execute and imagine simple wrist flexion/extension while fMRI data were recorded (Lehericy et al., 2004). This study showed abnormal activity in parietal and frontal regions in patients with respect to controls during both motor imagery and execution (Lehericy et al., 2004). Using the same task and technique, a later study investigated the neural correlates of motor imagery in patients suffering from dystonia due to complex regional pain syndrome (Gieteling et al., 2008). The results showed that with respect to healthy controls, motor imagery of wrist flexion/extension in these patients was associated with a reduced activation in fronto-parietal cortex (Gieteling et al., 2008). Consistent data have been recently reported in two paired studies. In these studies, FHD patients were asked to perform motor imagery of grasping a pencil with the purpose of either write with it or sharpen it (Delnooz et al., 2013, Delnooz et al., 2012). In the first study, the authors individuated the pattern of brain activity, and showed that with respect to controls, FHD patients had stronger activity in premotor areas during imagery of grasping for writing but not during imagery of grasping for sharpening (Delnooz et al., 2013). These data suggest that in the region typically involved in balancing the motor output as a function of the sensory feedback, some degrees of abnormalities already exist at the level of movement planning or calibration. In the second study the authors applied a functional connectivity approach to the same dataset to further understand the interplay between the previously individuated regions of interest (Delnooz et al., 2012). This study showed that FHD patients had reduced connectivity between the premotor cortex and the parietal cortex with respect to controls (Delnooz et al., 2012). Taking into account that in healthy controls the coupling between premotor and parietal cortices is important for movement simulation and calibration (de Lange et al., 2006) and that the parietal cortex is an important hub for integrating information coming from different modalities (e.g. visual and motor; Fogassi and Luppino, 2005), the reduced functional connectivity between parietal and premotor cortex could be associated with a decreased ability to sample sensory feedback and integrate it with movement execution. However, these results should be considered with caution in the absence of a quantitative measurement of the patients' imagery performance.

Neuroimaging studies based on previous models showed the involvement of both cortical and subcortical regions, suggesting that dystonic deficits affect a broadly distributed network but leaving

unsolved the issue of which nodes of this network are specifically impaired. The inconsistencies in the available results could be due to methodological differences in experimental protocols, required tasks, scanning procedures, or the under-estimation of the distorted sensory feedback as a crucial confounding factor that renders the investigation of sensorimotor processes particularly difficult. Conversely, mental rotation of body parts engages anatomically interconnected brain systems implicated in the integration of sensorimotor information and has been implemented with brain imaging for studying the properties of the sensorimotor system in movement disorders such as Parkinson's disease. However, both neuroimaging and physiological data necessary to identify the pathophysiological peculiarities of FHD are still lacking, and mental rotation is a good tool to acquire this information. This important information on brain activity and cortico-spinal communication relative to mental rotation of body parts in FHD represents an unresolved gap that could and should be filled. Finding the influence of FHD in modulating the activity of specific neural circuits, such as hypersynchronous activity, might help not only to better understand the pathophysiology of FHD, but also to develop ad-hoc interventions aiming at further regulating those brain circuits.

In addition, patients who lost their dominant limb due to amputation, show longer latencies and lower accuracy in the mental rotation of images depicting the amputated hand (Nico et al., 2004), therefore presenting highly specific impairments. The debate on the specificity of this effects has been further addressed taking into account the mental rotation performance of patients in which one or both hands never developed from birth, i.e. bilateral or unilateral amelia (Funk and Brugger, 2008). As in cerebral palsy, bilateral amelia results in a general slowing down, but does not affect the general modulation of the response times as a function of the stimulus orientation. Similar to amputees, unilateral amelic patients' performance is slower for the missing hand with respect to the present hand.

In cervical dystonia (affecting the neck and therefore the vestibular system) mental rotation of all body parts is impaired (Fiorio et al., 2007b), while in FHD (affecting only one specific body segment) the mental rotation of only the affected hand is selectively impaired (Fiorio et al., 2006). In a later study Katschnig et al. (2010) used mental rotation to investigate the differences between fixed and mobile dystonia. By showing that fixed dystonia (more debilitative) elicits longer latencies than mobile dystonia (less debilitative), their data confirmed that the severity of impairment is reflected in mental rotation abilities (Katschnig et al., 2010).

Based on these data it could be concluded that, regardless of the general availability of sensory feedback, the most crucial factor influencing mental rotation is body asymmetry, suggesting that the sensorimotor system tends to put more weight on the available information with a consequent detriment for the representation of the affected body part.

A way to test this possibility takes into account the mechanisms of postural and proprioceptive online recalibration. In healthy subjects, congruent visuo-tactile stimulation promotes self-attribution of a fake hand as explicitly measured by self-reports (“rubber hand illusion”), but does not necessarily affect proprioceptive hand recalibration as implicitly measured by the “proprioceptive drift” procedure (Rohde et al., 2011). Possibly due to such implicit-explicit dissociation, in FHD the illusory self-attribution is preserved but the proprioceptive drift is impaired (Fiorio et al., 2011). However, it is not clear whether the absence of proprioceptive drift in FHD is due to measurement (in)sensitivity or to aberrant sensorimotor plasticity. The possibility to quantitatively measure the behavioral outcomes of the plasticity of sensorimotor representations is provided by mental rotation. Indeed, in healthy subjects the illusory self-attribution due to the RHI correlates with the performance in such mental transformations, even in the absence of proprioceptive drift (Ionta et al., 2013). Nevertheless, despite the fact that such measurements might provide a less controversial measurement of proprioceptive hand recalibration in FHD, no data are currently available.

6. Clinical application 2: Biomimetic Brain-Machine Interfaces

Every year in the United States of America alone about two million people suffer from the consequences of spinal cord injury (250 thousand; Jackson et al., 2004) or limb loss (1.6 million; Ziegler-Graham et al., 2008). These, and other similar breakdowns in communication between the central nervous system and the body's periphery, result in a complex picture of symptoms including motor and/or somatosensory impairments. Despite the great technological developments in spinal cord repair (Tabakow et al., 2014, van den Brand et al., 2012) and even if some of the most advanced approaches are currently undergoing human clinical trials (Wang et al., 2014), the new solutions are still far from being implemented as a part of standard rehabilitation procedures. Until clinical and non-clinical researchers identify treatments for each of these conditions and learn how to re-establish functions of a disconnected or uncontrolled limb, patients will continue to tirelessly await novel solutions to re-acquire even the slightest part of their former mobility and autonomy.

Brain-machine interfaces (BMIs) are an alternative approach that proposes bypassing the lesion or substituting the involved body segment and aims to restore at least part of the sensorimotor functions in patients suffering from movement disorders due to disconnection or loss. BMIs decode neural activity associated with motor intentions directly from the brain or nerves and feed it into an assistive device (see also Rupp et al., 2014). One of the most obvious applications is the control of robotic prostheses based on brain activity. For example, electrocorticography (ECoG) can be used to record brain activity associated with a particular movement, and a BMI system can decode these patterns of neural activity and translate them into commands for a prosthetic device able to perform the corresponding movement (Marquez-Chin et al., 2009). The first occurrence of the BMI concept can be attributed to the group guided by E. E. Fetz who demonstrated how robotic devices could be controlled by brain activity (Fetz, 1969, Fetz and Finocchi, 1971, Fetz and Baker, 1973). In the same years J. J. Vidal described a BMI system based on electroencephalography (EEG), thus highlighting the feasibility of non-invasive techniques for the control of prosthetic devices (Vidal, 1973). The following forty years have been marked by intensive worldwide research and growth of the field at an astonishing pace. The capabilities and features of BMI systems have considerably broadened, relying on a panel of different biological signals and aiming at the treatment of an increasing number of clinical conditions (Wolpaw et al., 2006, Mak and Wolpaw, 2009). After an initial phase of development and testing, BMI technologies have finally left the laboratory and are nowadays starting to get deployed to patients' living places for daily activities (Vaughan and Wolpaw, 2006, Sellers et al., 2010). This became strikingly clear with the first kick being shot by a paraplegic patient using a full EEG-controlled exoskeleton at the opening ceremonies of the Football World Cup

2014 (Nicolelis, 2012, Nicolelis and Servick, 2014). Thus, BMIs are not only reaching specific clinical populations, but also gradually entering the collective consciousness of the wider public.

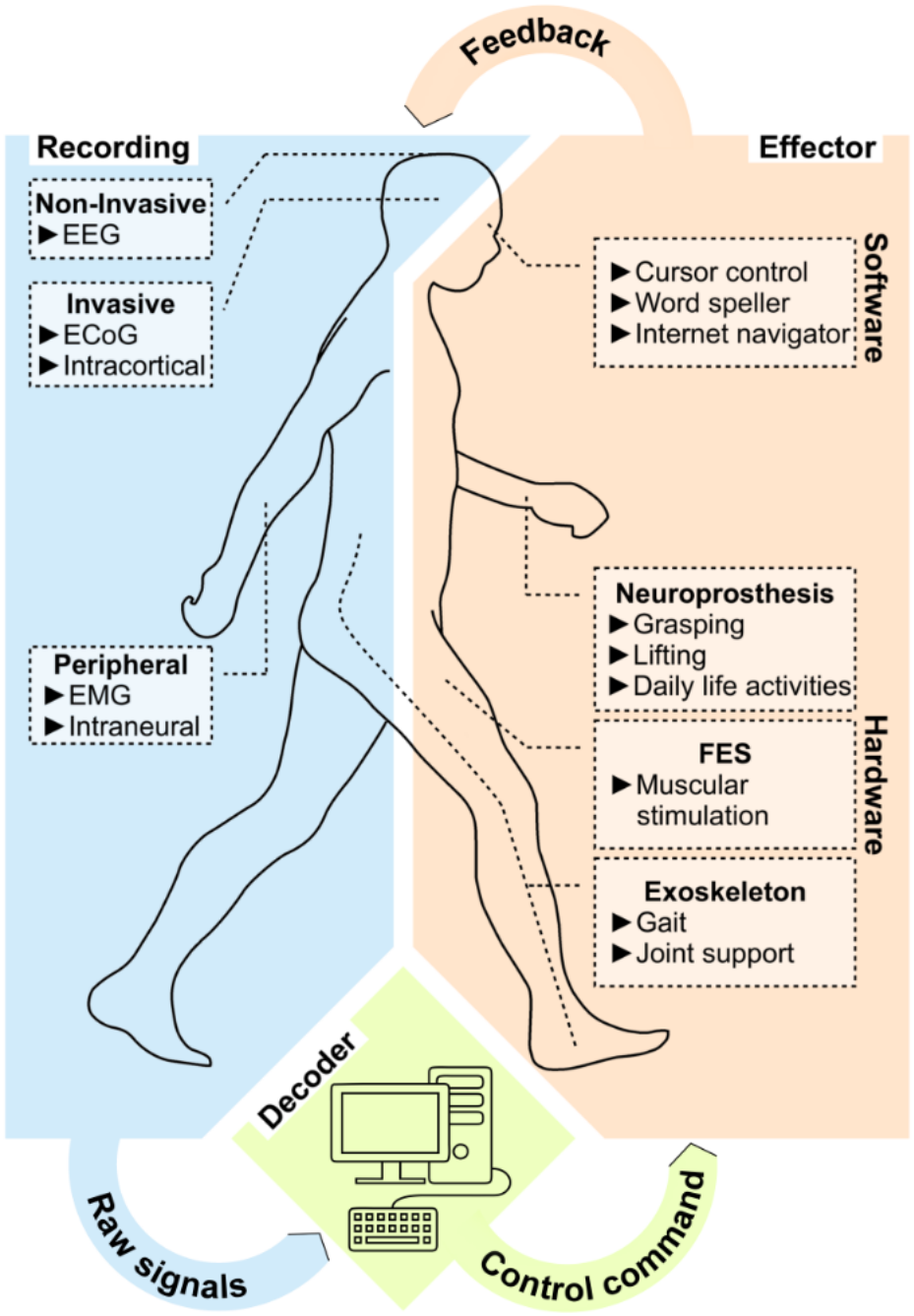
Here, we focus on the importance of generating matching somatosensory percepts when designing BMIs to restore lost motor functions. First, we address the importance of properly classifying users and selecting correspondingly appropriate BMIs. Next, we review the state-of-the-art developments in substitutive BMIs, including the different types of biological signals that can be used and their respective applications. Finally, we discuss current approaches for providing sensory feedback to and from BMIs, with a specific focus on how biomimetics principles can increase incorporation and control by the artificial reproduction of normal neural mechanisms.

6.1. User-BMI integration

The first important step in clinically-applied BMIs is the classification of users in order to select the best fit between the user's needs and the available BMI solutions. Because the same BMI approach can address similar symptoms despite very different etiologies, the best user-BMI match could be based on the disease effects (Wolpaw et al., 2006). According to this method, patients' conditions and needs can be differentiated into three categories. The first group comprises patients who present mild and/or localized motor impairments and maintain most volitional movements. For this class of users, BMI technology likely has limited benefit since their residual muscular activity is sufficient to effectively control any potential assistive device. The second class includes patients who retain some degrees of volitional motor activity and require a specifically customized BMI system. For example, high cervical spinal cord injury preserves only extremely meager voluntary control, and patients could benefit from a hybrid EMG/BMI system. Finally, the third group consists of patients with no volitional motor activity, who rely entirely on BMI even for elementary tasks. Locked-in syndrome is one example of this class of patients who can profit from BMI systems even for basic communication. However, locked-in syndrome represents a particularly difficult case, because patients' performance in BMI control is generally below the normal average. The exact reason for this inefficacy is not fully understood yet, but potential causes include impaired vision and cognitive disability (Birbaumer, 2006). These factors might also be the origin of a sort of "illiteracy" for brain-computer interfaces, a condition affecting between 15% and 30% of the users (Guger et al., 2003, Vidaurre and Blankertz, 2010) and consisting in the inability to modulate brain signals and therefore to profit from brain-computer interfaces applications. One possible solution to this issue is to rely on the so-called "co-adaptivity", in which both user and BMI system dynamically adapt to each other (Millán et al., 2010, Wolpaw and Wolpaw, 2012). To allow this continuous side-by-side enhancement,

the BMI system must regularly update its decoding algorithm based on newcomer neural data from the user. Reciprocally, the user needs to be presented with feedback of the BMI performance, from which he can optimize its mental strategies. In most cases, this closed-loop system results in steeper learning curves and/or generally improved BMI efficiency (Mattout et al., 2015, Bryan et al., 2013).

How can co-adaptivitiy be further optimized? By aiming at the preservation of the mapping between naturally-evoked neural activity and sensorimotor features of limb state and control, the concept of "biomimicry" has emerged as a possible solution (Bensmaia and Miller, 2014). The exploitation of biomimetic principles had been applied for the optimization of both BMI control and feedback. In the former case, an example of such application is attempting to decode limb endpoint velocity or position naturally encoded into brain activity during execution or imagination of movement (Flint et al., 2012, Fan et al., 2014). From a sensory feedback point of view, biomimicry attempts to artificially recreate neural activity naturally-occurring during normal sensory experience. Probably the most widely spread systems following this approach are cochlear implants, which aim at exciting the cochlea with matching spatial, temporal and spectral features of normal auditory signals (Wander and Rao, 2014), but several other techniques, mostly cortical stimulations, have been applied in a similar prospect (Berg et al., 2013, Tabot et al., 2013). By relying on natural neural schemes, biomimetic systems also tend to be experienced more intuitively by the users, facilitating their acceptance and easing their integration into daily routines. This acceptance depends on the user's sense of being in control of the device (agency, see section 6.2) as well as the sense that the device belongs to the user's body (ownership, see also section 6.3 and 6.4).



From:
Pisotta, Perruchoud et Ionta, (2015)

Figure 9: **The brain–BMI–brain loop**. Schematic representation of the neuro-computational circuitry between the different possible techniques for acquiring neural signals (in blue, left panel), computational decoders (in light green, lower panel), and devices (in orange, right panel). First, in the "recording" phase, the brain activity is recorded through invasive or non-invasive methods, resulting in the transmission of raw signals to the next phase. Second, during the "decoder" phase, the neural signals are decoded and classified by machine-learning adaptive algorithms, which generate control commands to be sent to the external tool. Third, in the "effector" phase, the resulting computational output is used to control different kind of hardware and software devices. Finally, the device sends feedback signals back to the brain (upper arrow).

6.2. Neuroprosthetic Control

After the best user-BMI integration is identified, users must be provided with intuitive control of BMI devices in order to allow a full incorporation of the prosthesis into the user's body schema (a mental representation of the shape, posture, and anatomical constraints of one's own body; Berlucchi and Aglioti, 2010). To this aim, it is necessary to develop the sense of being in control of the prosthesis device, taking advantage of the behavioral and neurophysiological outcomes of movement representation as a function of physical training (Ionta et al., 2010a). Hereafter, we define "control" as the ability to voluntarily change the states of a dynamic system in order to achieve specific tasks and desired goals. This can refer to different levels of organization in robotic prosthetics (Tucker et al., 2015). The most common prosthetic control relies on the extraction of specific features of electroencephalographic (EEG) brain signals and the translation of relevant features into commands for the neuroprosthetic device or into triggers for muscular contraction (Wolpaw et al., 2002). In patients with residual voluntary muscle control, many other sources can be exploited in addition to brain activity,, such as electromyography (Memberg et al., 2014, Ambrosini et al., 2014, Scheme and Englehart, 2011) or electroculogram (Usakli et al., 2010). The procedures for extracting all the different signals can be grossly split into invasive and non-invasive techniques.

6.2.1. Non-invasive techniques

Electrophysiological or metabolic brain signals are detectable using a wide range of non-invasive techniques. Scalp EEG is currently the most common technique for BMI applications (Bortole et al., 2014), and is capable of detecting specific time-frequency patterns of brain activity associated with voluntary or involuntary cognitive and sensorimotor processing (Wolpaw et al., 2002) . The wide varieties of signals that can be measured from EEG, together with its low cost, portability, and compliance by a range of participants, make EEG a particularly attractive technique for BMIs. Nevertheless, EEG signals detected on the scalp can be greatly distorted (e.g. by the resistance of the skull), resulting in a massive drop in spatial resolution. Advanced decoding algorithms can nevertheless greatly improve the information gathered from scalp recording, and rivaling with more invasive techniques (Wolpaw and McFarland, 2004). This feature, together with relatively affordable price, compliance, and high temporal resolution, makes of EEG one of the ideal candidates to supply the information on cortical activity to the BMI systems. In one of the latest designs, EEG-based BMIs have been used to move wheelchairs (Carlson and Millán, 2013), spell words (Yin et al., 2013, Hwang et al., 2012), and estimate hand (Bradberry et al., 2010) and locomotion kinematics (Presacco et al., 2011). Building on the effectiveness of mental simulation in activating specific neural mechanisms

(Ionta and Blanke, 2009, Ionta et al., 2010b), it has been shown that simulating hand and foot movements enables BMI control (McFarland et al., 2010). Real-time brain activity can be accessed also with other techniques such as functional magnetic resonance imaging (Ruiz et al., 2014), magnetoencephalography (Buch et al., 2008, Mellinger et al., 2007), or near-infrared spectroscopy (Coyle et al., 2007, Sitaram et al., 2007, Power et al., 2011). These techniques have better spatial resolution, but are unpractical in daily-life situations. Therefore, they are used mostly for therapeutic purposes in clinical settings, e.g. neural activity modulation (Broetz et al., 2010). Nevertheless, those approaches can potentially contribute to the improvement of BMI performance when coupled with EEG (Fazli et al., 2012, Quandt et al., 2012).

6.2.2. Invasive techniques

Invasive techniques tend to provide less noisy signals with better spatial resolution, with respect to non-invasive methods. However, they present downsides due to surgical implantation, limited number of channels, risk of infection, and cellular isolation or death. The most common invasive techniques are intraneural recording, electrocorticography (ECoG), and intracortical electrodes. Being directly inserted inside the nerve fascicles, intraneural electrodes can record peripheral activity in patients without spinal nor nerve damages, such as amputees (Rossini et al., 2010, Micera et al., 2010a, Micera et al., 2010b). These systems can exploit biologically relevant tasks, such as natural grasping (Micera et al., 2011, Di Pino et al., 2012). Allowing direct recording from the surface of the brain, ECoG relies on the same principles as EEG, but avoids signal blurring by surgically inserting grids or stripes of subdural electrodes onto the cortex. Similarly to EEG, it can be used to control a wide variety of devices for assistive technology (Leuthardt et al., 2004). For example, ECoG-BMI has been successful in controlling one-, two-, or three-dimensional software implementations (Leuthardt et al., 2011, Milekovic et al., 2012, Schalk et al., 2008, Wang et al., 2013), or decoding natural motor intentions (Spuler et al., 2014). So far, ECoG-BMI experimentation has been restricted to animal studies or temporary pre-surgical ECoG implants (Leuthardt et al., 2004). However, recent studies show that ECoG can be implemented for the recovery of motor functions for severely paralyzed patients (Wang et al., 2013). Finally, intracortical recording is based on the surgical insertion of high-density electrode microarrays in the cortical layers (Campbell et al., 1991). These electrodes can record neural activity at the single cell level. BMI experimental investigations have been carried out in non-human mammals (Serruya et al., 2002, Carmena et al., 2003, Velliste et al., 2008, O'Doherty et al., 2009, O'Doherty et al., 2012, Venkatraman et al., 2009, Flint et al., 2012, Ethier et al., 2012, Bansal et al., 2012). Almost exclusively pilot trials of intracortical

recording have been performed in humans (Collinger et al., 2013, Hochberg et al., 2012, Hochberg et al., 2006, Simeral et al., 2011). This particular technique raises the issue of long-term signal stability, as signal quality tends to decrease with time, due to the emergence of inflammation and fibrotic tissues that isolate the electrodes as a natural immune response of the neuroglia (Polikov et al., 2005). Nevertheless, a new-generation of biocompatible flexible electrodes decreases the risk of rejection and provides stable signals for longer periods (Marin and Fernandez, 2010). The most notable recent applications of intracortical BMI for humans include giving a tetraplegic patient a point-and-click ability up to 1'000 days after implantation (Simeral et al., 2011), or the natural control of a 7 degrees-of-freedom neuroprosthesis (Collinger et al., 2013, Hochberg et al., 2012).

Altogether, multiple approaches can be considered for BMI control, each of which being suitable for a different population of patients. The highest BMI performance are still obtained using invasive recording techniques, but recent advances in EEG signal processing are rapidly filling the gap and might provide similar results within a cheap, non-invasive, and perfectly safe framework in the upcoming decades.

6.3. Biomimicry of Sensory Feedback

The previous section highlighted how an ideal BMI should translate brain signals encoding movements into computational commands to activate mechanical movements (Pistohl et al., 2012). However, not only pure motor disorders, but also deficits associated with sensory loss can dramatically affect movement execution (Sainburg et al., 1995). Thus, a real-time feedback of the prosthetic movement should be provided to the user in the form of artificial sensory consequences (Yanagisawa et al., 2012). Based on this feedback, on the one hand the user can learn to adjust his brain activity according to the performance of the device by identifying and exploiting appropriate mental strategies. On the other hand, the BMI system could use advanced machine learning algorithms to continuously adapt the prosthesis to the user (Vidaurre et al., 2011) and could also receive real-time feedback of its own performance through, for example, the detection of error-related brain activity patterns (Ferrez and Millán, 2005, Ferrez and del, 2008, Chavarriaga and Millán, 2010, Combaz et al., 2012). Thus, the creation of sensory consequences of a prosthetic action has a crucial role in the deployment of successful BMIs. In order to close this user-BMI-user loop, efficient control and real-time feedback have to be properly integrated (Pisotta et al., 2015). In the same vein, cognitive neuroscience has shown that coherent low-level sensory information (e.g. vision and touch) is essential for building high-level psychological constructs such as body ownership (Botvinick and Cohen, 1998). In the so-called "rubber hand illusion", Botvinick et al. created illusory hand ownership

through synchronous stimulation of a fake hand (visual) and the participant's real hand (tactile). The same effect has been demonstrated with non-anthropomorphic robotic hand prosthesis (Rosen et al., 2009). Recent evidence showed the importance of congruent visuo-tactile information to properly represent our body (Ionta et al., 2013). Accordingly, by promoting the sense of prosthesis ownership, congruent visuo-tactile stimulation can lead to its acceptance and recognition as part of one's own body (Marasco et al., 2011).

The effective implementation of sensory feedback in standard BMIs still requires technological developments to produce well-balanced closed-loop systems. In most current BMIs, this balance cannot be reached because of unnatural or modality-mismatching feedback. Typically, this feedback consists only in a mere movement observation. But, vision alone does not provide important information on e.g. pressure, texture, stiffness, slipperiness, weight, etc. These features are continuously extracted during object manipulation and are mediated by the appropriate somatosensory afferents. Additionally, vision does not allow fine-tuned movement recalibration based on proprioception, an inescapable source of information to properly interact with the environment. Finally, visual information is pointless during isometric muscle activity, in which a modulation of the applied force does not translate into actual movement (for example while grasping a stiff object with increasing force). Thus, despite the undisputable importance of vision for motor performance (Flanagan and Johansson, 2003, Johansson et al., 2001, Johansson and Flanagan, 2009), visual feedback alone cannot satisfy the requirements for the effective manipulation of a neuroprosthesis. The need for somatosensory feedback, including proprioception, is considered one bottleneck for application of BMIs (Lebedev and Nicolelis, 2006). As depicted by the SMILE model, the interaction between somatosensory and motor processing is inherent at several stages of motor control, including cortical and subcortical networks (Pisotta and Molinari, 2014), and strongly relies on the multifaceted complexity (Saal and Bensmaia, 2014) and extremely high spatial resolution of tactile information (Skedung et al., 2013).

The artificial reproduction of natural somatosensory consequences of a motor act can be considered as a component of the so-called biomimicry: the preservation of the mapping between naturally-evoked neural activity and healthy sensorimotor limb features. Along these lines, BMI systems are nowadays being designed with the aim of naturally interacting with the user, including the possibility of providing somatosensory signals (Ramos-Murguialday et al., 2012). The transition from visual to a more motor-relevant somatosensory feedback is starting to show its first results. Building on previous evidence on the effectiveness of mental simulation in activating sensorimotor pathways (Fourkas et al., 2006), Cincotti et al. (2007) integrated either visual or vibrotactile real-time feedback while participants mastered their brain activity by simulating hand movements. Vibrotactile

feedback yielded better results in situations where the visual channel was heavily loaded and all participants reported a more natural feeling while using vibrotactile feedback. This subjective preference for tactile feedback might arise from the tight relationship between the motor and somatosensory systems (Perruchoud et al., 2014). Similarly, ipsilateral matching mental simulation and tactile feedback yield better performance, suggesting that a non-biomimetic contralateral feedback generates an interference (Chatterjee et al., 2007). Moreover, the use of pressure gradient (instead of vibrotactile feedback) tends to match more closely the neural process of feedback occurring during normal motor action, therefore increasing biomimicry leads to better performance, supporting that that grip recognition relies on the ability to recognize both finger configurations and pressure levels (Antfolk et al., 2013a). In summary, the reviewed findings support that proper user-BMI integration depends also on the identification of the proper and patient-customized selection of biomimicry-relevant feedback, with different learning curves for each modality.

6.4. Biomimetic (invasive) Somatosensory Substitution

The reviewed advances in BMI feedback raised the possibility to completely bypass a defective sensory organ and directly stimulate (upstream) the nervous system. We already introduced intraneural recording of peripheral activity. A similar technology can be used to stimulate peripheral nerves and elicit sensory percepts. For example, Di Pino and colleagues (2012) implanted intraneural electrodes in an amputee experiencing phantom pain, a chronic and continuous painful sensation from the missing limb (Knecht et al., 1996). Intraneural stimulation replaced the absent afferent signals corresponding to somatosensory consequences of movements, and the patient reported diminished phantom pain and increased performance (Di Pino et al., 2012). Using a similar setup, Raspopovic et al. (2014) enhanced the identification of postures, shapes, and stiffness in the absence of visual and auditory information, suggesting the incorporation of the BMI system into the user's body representation. Finally, sparse vibrotactile stimulation during neuroprosthetic object manipulation helps patients to efficiently regulate movement control (Cipriani et al., 2014).

Recently it has become feasible to bypass not only specific body segments but also the entire peripheral nervous system and directly stimulate cortical areas to elicit somatosensory percepts. Such an intracortical stimulation approach has been performed mostly in animal models, for example, using optogenetics. In optogenetic experiments, animals are genetically engineered to grant the possibility to modulate brain activity (at high spatial and temporal resolution) using brain implanted optical fibers (Zemelman et al., 2002). Using this technique, O'Connor et al. (2013) elicited an illusory and robust perception of obstacle. Another solution to elicit a much broader panel of

percepts is via so-called "intracortical microstimulation" (ICMS). It is based on the same principles of intracortical recording, but employs electrodes arrays instead of single electrodes (Romo et al., 1998). Using ICMS, sensations can be elicited by stimulating specific cortical areas with particular parameters. For example, after vibrotactile-ICMS training, owl monkeys are able to solve a binary forced-choice task to get a reward, solely based on specific patterns of ICMS cues (Fitzsimmons et al., 2007).

Classic intracortical stimulation and ICMS can be carried out over longer periods with respect to intracortical recording, because the electrodes' physiologic isolation due to fibrotic tissues can be circumvented by modulating the stimulation parameters (Bensmaia and Miller, 2014). In the same vein, the first bi-directional ICMS-based BMI showed that rhesus monkeys can control a cursor (based on signals from motor cortex) while the task consequences are encoded as specific ICMS patterns in the sensory cortex (O'Doherty et al., 2009). As an extension of this study, the same approach has also been used to control more complex situations such as virtual hands (O'Doherty et al., 2012). Treated animals become able to identify virtual textures within the same time-scale as for natural tactile exploration (Lebedev et al., 1994, Liu et al., 2005). Similarly, ICMS can be used to faithfully encode skin indentation and then render native and prosthetic body parts more equivalent in terms of tactile discrimination (Berg et al., 2013), location, pressure, and timing (Tabot et al., 2013). Finally, ICMS can augment perceptual abilities, e.g. invisible (infrared) inspection, by regulating intracortical stimulation as a function of signals created by implanted infrared detectors (Thomson et al., 2013).

A further alternative to classic BMI technology is "targeted reinnervation", which is demonstrating robust results in restoring sensorimotor functions. This technique allows for the re-implantation of residual nerves after amputation into denervated muscles (Kuiken et al., 2004, Kuiken et al., 2009). Typically, after arm amputation, the remaining arm nerves are redirected and re-implanted into the denervated ipsilateral chest area, creating a bidirectional communication channel. By redirecting the previously healthy nerves terminations, the neural patterns involved in motor control and sensory feedback are conserved, and the biomimicry of the system is therefore maintained. Downstream, voluntary motor commands are sent to the amputated arm and produce muscular activity in the reinnervated chest muscles, who function as bio-amplifiers and translate neural information into prosthetic commands. Upstream, afferent channels can transmit information from the reinnervated mechanoreceptors (in the chest) to the brain regions representing the amputated limb. This allows tactile stimulation of the chest to be experienced as emanating from the amputated arm (Kuiken et al., 2007). This innovative technique initiated a substantial improvement in the complexity and biomimicry of robotic prostheses. Sensitivity comparisons showed that grating

identification and force level are as accurate with reinnervated skins as normal skin (Marasco et al., 2009) and equal or better in point localization (Sensinger et al., 2009, Marasco et al., 2009). In addition, when comparing targeted reinnervation with other current neuroprosthetic approaches, the sense of ownership for a prosthetic device is increased (Marasco et al., 2011), and prosthetic movements are simplified thanks to better fine-tuned visuo-tactile matching (Kim and Colgate, 2012). The current challenge is to encode somatosensory information from the prosthetic arm and intelligibly transmit it to the reinnervated area. These examples highlight the need of constant development of engineering solutions and improvement of existing sensors that are able to detect a broad range of relevant signals (for example different degrees of shearing, pressure, temperature and humidity), such as the artificial skin recently developed by Kim and coll§eagues (2014).

6.5. Current Limitations and Future Challenges

Recent technological and scientific advances have considerably extended the field of sensory feedback for neuroprosthesis, but a natural perception requires a more precise combination of parameters such as frequency, duration, intensity, temporal patterns, and localization (Cincotti et al., 2007, Bensmaia and Miller, 2014). Specific combinations of features might elicit a broad range of different percepts and the complete mapping of all parameter combinations with the corresponding percept in animals can be extremely laborious, if not impossible. Conversely, this process can be reverse-engineered in humans, by having the participant reporting the sensation elicited by exhaustive combinations of features, and identifying the corresponding combination for each investigated sensory feedback. Thus future directions will have to attempt the transition from animal research to human clinical trials.

A recent advance with eminent fallouts on neuroprosthetics and neurorehabilitation is immersive virtual or augmented reality. An augmented reality feedback is more engaging and challenging than a simplistic visual depiction (Chin et al., 2010). Accordingly, also illusory body ownership (rubber hand illusion) can be triggered for virtual arms, with remarkable outcomes both at the behavioral (Perez-Marcos et al., 2009) and neural level (Evans and Blanke, 2013). Virtual reality-based BMI systems have critical implications for rehabilitation (Bermudez i Badia et al., 2013), suggesting that, by increasing the visual biomimicry of BMI systems, virtual and augmented reality could augment patients' involvement in rehabilitation protocols and therefore improve sensorimotor recovery. The implementation of haptic feedback in (currently exclusively visual or audio-visual) virtual reality setups would add precious input to be able to re-create a broad range of natural percepts in an immersive manner.

Not only physical tasks can be improved by augmenting the biomimicry of BMIs, but also neurological condition such as phantom pain or phantom referral tactile sensation. The former is believed to originate from incoherent experience with respect to the body representation, the latter arises from reinnervation and/or cortical reorganization. For example, the proximity of the hand and face areas in the cerebral cortex is probably the reason why many upper arm amputees get referral sensations in their phantom hand while stimulating their face. Thanks to biomimetic BMIs, a proper somatosensory stimulation can be associates with specific prosthetic movements, thus re-establishing a somatotopic correspondence between motor intentions and sensory feedback and therefore limiting sprouting of cortical maps (Antfolk et al., 2012, Antfolk et al., 2013b). Phantoms maps have been used to elicit illusory ownership sensations toward a rubber hand (Ehrsson et al., 2008) or a mechanical prosthesis (Rosen et al., 2009), and an fMRI study of the somatotopy of amputees highlighted the tight correspondence between somatotopic cortical maps of healthy individuals and phantom limb amputees (Bjorkman et al., 2012). The use of phantom-coherent somatosensory feedback decreases phantom pain, potentially by resolving multisensory discrepancy within body representation (Ramachandran and Altschuler, 2009).

6.6. The future steps of biomimetic BCI

The broad scope of BMI spreads across countless applications, including entertainment, monitoring physiological states (Lal et al., 2003), or augmenting physical and sensory abilities (Di Pino et al., 2014). In this chapter, we reviewed the existing literature on control and feedback for medical BMIs, with a special focus on the importance of biomimicry-relevant signals. The incorporation of the prosthesis in the user's body representation, including to his biological and psychological sense of self (Glannon, 2014), is a critical step for efficient rehabilitation, and is enhanced by engaging naturally-occurring control and sensory systems. An efficient incorporation of the device can be significantly reinforced via relevant somatosensory and proprioceptive feedback (Gallagher, 2005). However, artificially re-created sensory percepts risk to overload or distort the natural information processing (Lenay et al., 2003) and, in contrast to normal situations, are not constrained by modality-specific high-order mechanisms, including attention and cognition (Spence, 2014). This is one of the most challenging present limitations and, in order to control noisy and distracting signals as in natural conditions (reciprocal inhibition), future work will have to render BMIs able to self-regulate their activity as a function of attentional and cognitive states. This is why understanding and developing the concept of biomimicry with respect to the SMILE model will be crucial for the upcoming deployment of BMIs and their laboratory-to-user transition.

7. Conclusion: bringing back a SMILE

This thesis attempted to develop and test a novel biologically-based model of sensorimotor integration. This model is predominantly targeted at the understanding of sensorimotor disorders, by allowing the formulation and testing of clinically-relevant hypotheses, built upon the prevailing knowledge on symptomatic and pathophysiological mechanisms.

After identifying the different functional nodes required along the sensorimotor integration loop, we reviewed the available data in order to identify the most plausible neuroanatomical location for each of these nodes. To validate this hypothetical SMILE model, we performed two experiments investigating the motor component of the sensorimotor integration loop, via two different neuroimaging techniques. In addition to providing coherent outcomes with respect to the SMILE predictions, each of these studies also generated novel scientific proposals. For example, the fMRI experiment allowed us to identify a new role for EBA, which not only consists of a perceptual node, but also incorporates high-level bodily representations. Additionally, we could attest that global and local frames of reference while transforming bodily representations involves the activation of broadly divergent brain networks. Similarly, the TMS experiment resulted in critical information about the timing of the motor phase of the well-known hand laterality judgment task, and allowed us to validate a novel paradigm to deal with the high inter- and intra-subject variations of behavioral performances, which had – in our knowledge – never been investigated. In the last sections of this manuscript, we present two potential clinical applications of the SMILE model, (1) by proposing two SMILE-derived hypotheses on the neural origin of focal hand dystonia, and (2) by highlighting how a steady understanding of the sensorimotor integration process can have critical implication in the development of cutting-edge technologies, such as brain-machine interfaces.

In fine, the SMILE model appears to be a potent tool to operate when investigating sensory and/or motor processes, but as any existing model, it need to be further validated, particularly regarding its sensory components that were not covered by the scope of this thesis. As any existing model, it should also be constantly challenged and extended in the light of novel scientific evidences. For example, no biological system works in perfect isolation, and the sensorimotor system is no exception to this rule; as presented in the last chapter, other senses than somatosensation – such as vision and audition – can also play an essential role in directing movement, yet their implications are critically absent from the SMILE. A future extension of the model could quantify these new interactions and localize their impacts on each of the current nodes, pushing the understanding of sensorimotor integration, one more step further.

8. References

ABBRUZZESE, G. & BERARDELLI, A. 2003. Sensorimotor integration in movement disorders. *Mov Disord,* 18**,** 231-40.

AGLIOTI, S. M., FIORIO, M., FORSTER, B. & TINAZZI, M. 2003. Temporal discrimination of cross-modal and unimodal stimuli in generalized dystonia. *Neurology,* 60**,** 782-5.

ALTENMULLER, E. & JABUSCH, H. C. 2010. Focal dystonia in musicians: phenomenology, pathophysiology and triggering factors. *Eur J Neurol,* 17 Suppl 1**,** 31-6.

AMBROSINI, E., FERRANTE, S., SCHAUER, T., KLAUER, C., GAFFURI, M., FERRIGNO, G. & PEDROCCHI, A. 2014. A myocontrolled neuroprosthesis integrated with a passive exoskeleton to support upper limb activities. *J Electromyogr Kinesiol,* 24**,** 307-17.

ANTFOLK, C., BJORKMAN, A., FRANK, S. O., SEBELIUS, F., LUNDBORG, G. & ROSEN, B. 2012. Sensory feedback from a prosthetic hand based on air-mediated pressure from the hand to the forearm skin. *J Rehabil Med,* 44**,** 702-7.

ANTFOLK, C., CIPRIANI, C., CARROZZA, M. C., BALKENIUS, C., BJORKMAN, A., LUNDBORG, G., ROSEN, B. & SEBELIUS, F. 2013a. Transfer of tactile input from an artificial hand to the forearm: experiments in amputees and able-bodied volunteers. *Disabil Rehabil Assist Technol,* 8**,** 249-54.

ANTFOLK, C., D'ALONZO, M., ROSEN, B., LUNDBORG, G., SEBELIUS, F. & CIPRIANI, C. 2013b. Sensory feedback in upper limb prosthetics. *Expert Rev Med Devices,* 10**,** 45-54.

ARGYELAN, M., CARBON, M., NIETHAMMER, M., ULUG, A. M., VOSS, H. U., BRESSMAN, S. B., DHAWAN, V. & EIDELBERG, D. 2009. Cerebellothalamocortical connectivity regulates penetrance in dystonia. *J Neurosci,* 29**,** 9740-7.

BANSAL, A. K., TRUCCOLO, W., VARGAS-IRWIN, C. E. & DONOGHUE, J. P. 2012. Decoding 3D reach and grasp from hybrid signals in motor and premotor cortices: spikes, multiunit activity, and local field potentials. *J Neurophysiol,* 107**,** 1337-55.

BARA-JIMENEZ, W., CATALAN, M. J., HALLETT, M. & GERLOFF, C. 1998. Abnormal somatosensory homunculus in dystonia of the hand. *Ann Neurol,* 44**,** 828-31.

BARA-JIMENEZ, W., SHELTON, P. & HALLETT, M. 2000. Spatial discrimination is abnormal in focal hand dystonia. *Neurology,* 55**,** 1869-73.

BECK, S., SHAMIM, E. A., RICHARDSON, S. P., SCHUBERT, M. & HALLETT, M. 2009. Inter-hemispheric inhibition is impaired in mirror dystonia. *Eur J Neurosci,* 29**,** 1634-40.

BENSMAIA, S. J. & MILLER, L. E. 2014. Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. *Nat Rev Neurosci,* 15**,** 313-25.

BERG, J. A., DAMMANN, J. F., 3RD, TENORE, F. V., TABOT, G. A., BOBACK, J. L., MANFREDI, L. R., PETERSON, M. L., KATYAL, K. D., JOHANNES, M. S., MAKHLIN, A., WILCOX, R., FRANKLIN, R. K., VOGELSTEIN, R. J., HATSOPOULOS, N. G. & BENSMAIA, S. J. 2013. Behavioral demonstration of a somatosensory neuroprosthesis. *IEEE Trans Neural Syst Rehabil Eng,* 21**,** 500-7.

BERLUCCHI, G. & AGLIOTI, S. M. 2010. The body in the brain revisited. *Exp Brain Res,* 200**,** 25-35.

BERMUDEZ I BADIA, S., GARCIA MORGADE, A., SAMAHA, H. & VERSCHURE, P. 2013. Using a hybrid brain computer interface and virtual reality system to monitor and promote cortical

reorganization through motor activity and motor imagery training. *Neural Systems and Rehabilitation Engineering, IEEE Transactions on,* 21**,** 174-181.

BERNEISER, J., JAHN, G., GROTHE, M. & LOTZE, M. 2016. From visual to motor strategies: training in mental rotation of Hands. *Neuroimage*.

BEUKERS, R. J., VAN DER MEER, J. N., VAN DER SALM, S. M., FONCKE, E. M., VELTMAN, D. J. & TIJSSEN, M. A. 2011. Severity of dystonia is correlated with putaminal gray matter changes in Myoclonus-Dystonia. *Eur J Neurol*.

BHATIA, K. P. & MARSDEN, C. D. 1994. The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain,* 117 (Pt 4)**,** 859-76.

BIRBAUMER, N. 2006. Breaking the silence: brain-computer interfaces (BCI) for communication and motor control. *Psychophysiology,* 43**,** 517-32.

BJORKMAN, A., WEIBULL, A., OLSRUD, J., EHRSSON, H. H., ROSEN, B. & BJORKMAN-BURTSCHER, I. M. 2012. Phantom digit somatotopy: a functional magnetic resonance imaging study in forearm amputees. *Eur J Neurosci,* 36**,** 2098-106.

BLAKE, D. T., BYL, N. N., CHEUNG, S., BEDENBAUGH, P., NAGARAJAN, S., LAMB, M. & MERZENICH, M. 2002. Sensory representation abnormalities that parallel focal hand dystonia in a primate model. *Somatosens Mot Res,* 19**,** 347-57.

BLAKEMORE, S. J., WOLPERT, D. & FRITH, C. 2000. Why can't you tickle yourself? *Neuroreport,* 11**,** R11-6.

BLOOD, A. J., FLAHERTY, A. W., CHOI, J. K., HOCHBERG, F. H., GREVE, D. N., BONMASSAR, G., ROSEN, B. R. & JENKINS, B. G. 2004. Basal ganglia activity remains elevated after movement in focal hand dystonia. *Ann Neurol,* 55**,** 744-8.

BORICH, M. R., BRODIE, S. M., GRAY, W. A., IONTA, S. & BOYD, L. A. 2015. Understanding the role of the primary somatosensory cortex: Opportunities for rehabilitation. *Neuropsychologia,* 79**,** 246-55.

BORTOLE, M., CONTROZZI, M., PISOTTA, I. & UBEDA, A. 2014. BMIs for Motor Rehabilitation: Key Concepts and Challenges. *In:* JOSE, P. & DIEGO, T. (eds.) *Emerging Therapies in Neurorehabilitation.* Springer.

BOTVINICK, M. & COHEN, J. 1998. Rubber hands 'feel' touch that eyes see. *Nature,* 391**,** 756.

BRADBERRY, T. J., GENTILI, R. J. & CONTRERAS-VIDAL, J. L. 2010. Reconstructing three-dimensional hand movements from noninvasive electroencephalographic signals. *J Neurosci,* 30**,** 3432-7.

BREAKEFIELD, X. O., BLOOD, A. J., LI, Y., HALLETT, M., HANSON, P. I. & STANDAERT, D. G. 2008. The pathophysiological basis of dystonias. *Nat Rev Neurosci,* 9**,** 222-34.

BROETZ, D., BRAUN, C., WEBER, C., SOEKADAR, S. R., CARIA, A. & BIRBAUMER, N. 2010. Combination of brain-computer interface training and goal-directed physical therapy in chronic stroke: a case report. *Neurorehabil Neural Repair,* 24**,** 674-9.

BRYAN, M. J., MARTIN, S. A., CHEUNG, W. & RAO, R. P. 2013. Probabilistic co-adaptive brain-computer interfacing. *J Neural Eng,* 10**,** 066008.

BUCH, E., WEBER, C., COHEN, L. G., BRAUN, C., DIMYAN, M. A., ARD, T., MELLINGER, J., CARIA, A., SOEKADAR, S., FOURKAS, A. & BIRBAUMER, N. 2008. Think to move: a neuromagnetic brain-computer interface (BCI) system for chronic stroke. *Stroke,* 39**,** 910-7.

BUCKNER, R. L., ANDREWS-HANNA, J. R. & SCHACTER, D. L. 2008. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci,* 1124**,** 1-38.

BUTTERWORTH, S., FRANCIS, S., KELLY, E., MCGLONE, F., BOWTELL, R. & SAWLE, G. V. 2003. Abnormal cortical sensory activation in dystonia: an fMRI study. *Mov Disord,* 18**,** 673-82.

BYL, N. N. 2007. Learning-based animal models: task-specific focal hand dystonia. *ILAR J,* 48**,** 411-31.

BYL, N. N., MERZENICH, M. M., CHEUNG, S., BEDENBAUGH, P., NAGARAJAN, S. S. & JENKINS, W. M. 1997. A primate model for studying focal dystonia and repetitive strain injury: effects on the primary somatosensory cortex. *Phys Ther,* 77**,** 269-84.

BYL, N. N., MERZENICH, M. M. & JENKINS, W. M. 1996. A primate genesis model of focal dystonia and repetitive strain injury: I. Learning-induced dedifferentiation of the representation of the hand in the primary somatosensory cortex in adult monkeys. *Neurology,* 47**,** 508-20.

CAMPBELL, P. K., JONES, K. E., HUBER, R. J., HORCH, K. W. & NORMANN, R. A. 1991. A silicon-based, three-dimensional neural interface: manufacturing processes for an intracortical electrode array. *IEEE Trans Biomed Eng,* 38**,** 758-68.

CARLSON, T. & MILLÁN, J. D. R. 2013. Brain-controlled wheelchairs: a robotic architecture. *IEEE Robotics and Automation Magazine,* 20**,** 65-73.

CARMENA, J. M., LEBEDEV, M. A., CRIST, R. E., O'DOHERTY, J. E., SANTUCCI, D. M., DIMITROV, D. F., PATIL, P. G., HENRIQUEZ, C. S. & NICOLELIS, M. A. 2003. Learning to control a brain-machine interface for reaching and grasping by primates. *PLoS Biol,* 1**,** E42.

CEBALLOS-BAUMANN, A. O., PASSINGHAM, R. E., WARNER, T., PLAYFORD, E. D., MARSDEN, C. D. & BROOKS, D. J. 1995. Overactive prefrontal and underactive motor cortical areas in idiopathic dystonia. *Ann Neurol,* 37**,** 363-72.

CHASE, T. N., TAMMINGA, C. A. & BURROWS, H. 1988. Positron emission tomographic studies of regional cerebral glucose metabolism in idiopathic dystonia. *Adv Neurol,* 50**,** 237-41.

CHATTERJEE, A., AGGARWAL, V., RAMOS, A., ACHARYA, S. & THAKOR, N. V. 2007. A brain-computer interface with vibrotactile biofeedback for haptic information. *J Neuroeng Rehabil,* 4**,** 40.

CHAVARRIAGA, R. & MILLÁN, J. R. 2010. Learning from EEG error-related potentials in noninvasive brain-computer interfaces. *IEEE Trans Neural Syst Rehabil Eng,* 18**,** 381-8.

CHEN, R., WASSERMANN, E. M., CANOS, M. & HALLETT, M. 1997. Impaired inhibition in writer's cramp during voluntary muscle activation. *Neurology,* 49**,** 1054-9.

CHIN, Z. Y., ANG, K. K., WANG, C. & GUAN, C. 2010. Online performance evaluation of motor imagery BCI with augmented-reality virtual hand feedback. *Conf Proc IEEE Eng Med Biol Soc,* 2010**,** 3341-4.

CINCOTTI, F., KAUHANEN, L., ALOISE, F., PALOMAKI, T., CAPORUSSO, N., JYLANKI, P., MATTIA, D., BABILONI, F., VANACKER, G., NUTTIN, M., MARCIANI, M. G. & DEL, R. M. J. 2007. Vibrotactile feedback for brain-computer interface operation. *Comput Intell Neurosci***,** 48937.

CIPRIANI, C., SEGIL, J. L., CLEMENTE, F. & EDIN, B. 2014. Humans can integrate feedback of discrete events in their sensorimotor control of a robotic hand. *Experimental brain research,* 232**,** 3421-3429.

COLLINGER, J. L., WODLINGER, B., DOWNEY, J. E., WANG, W., TYLER-KABARA, E. C., WEBER, D. J., MCMORLAND, A. J., VELLISTE, M., BONINGER, M. L. & SCHWARTZ, A. B. 2013. High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet,* 381**,** 557-64.

COMBAZ, A., CHUMERIN, N., MANYAKOV, N. V., ROBBEN, A., SUYKENS, J. A. & VAN HULLE, M. M. 2012. Towards the detection of error-related potentials and its integration in the context of a P300 speller brain–computer interface. *Neurocomputing,* 80**,** 73-82.

COOPER, L. A. & SHEPARD, R. N. 1975. Mental transformations in the identification of left and right hands. *J Exp Psychol Hum Percept Perform,* 104**,** 48-56.

COYLE, S. M., WARD, T. E. & MARKHAM, C. M. 2007. Brain-computer interface using a simplified functional near-infrared spectroscopy system. *J Neural Eng,* 4**,** 219-26.

CRAIG, J. C. & KISNER, J. M. 1998. Factors affecting tactile spatial acuity. *Somatosens Mot Res,* 15**,** 29-45.

DE LANGE, F. P., HAGOORT, P. & TONI, I. 2005. Neural topography and content of movement representations. *J Cogn Neurosci,* 17**,** 97-112.

DE LANGE, F. P., HELMICH, R. C. & TONI, I. 2006. Posture influences motor imagery: an fMRI study. *Neuroimage,* 33**,** 609-17.

DE LANGE, F. P., JENSEN, O., BAUER, M. & TONI, I. 2008. Interactions between posterior gamma and frontal alpha/beta oscillations during imagined actions. *Front Hum Neurosci,* 2**,** 7.

DELMAIRE, C., VIDAILHET, M., ELBAZ, A., BOURDAIN, F., BLETON, J. P., SANGLA, S., MEUNIER, S., TERRIER, A. & LEHERICY, S. 2007. Structural abnormalities in the cerebellum and sensorimotor circuit in writer's cramp. *Neurology,* 69**,** 376-80.

DELNOOZ, C. C., HELMICH, R. C., MEDENDORP, W. P., VAN DE WARRENBURG, B. P. & TONI, I. 2013. Writer's cramp: Increased dorsal premotor activity during intended writing. *Hum Brain Mapp,* 34**,** 613-25.

DELNOOZ, C. C., HELMICH, R. C., TONI, I. & VAN DE WARRENBURG, B. P. 2012. Reduced parietal connectivity with a premotor writing area in writer's cramp. *Mov Disord,* 27**,** 1425-31.

DETANTE, O., VERCUEIL, L., THOBOIS, S., BROUSSOLLE, E., COSTES, N., LAVENNE, F., CHABARDES, S., LEBARS, D., VIDAILHET, M., BENABID, A. L. & POLLAK, P. 2004. Globus pallidus internus stimulation in primary generalized dystonia: a H215O PET study. *Brain,* 127**,** 1899-908.

DI PINO, G., BENVENUTO, A., CAVALLO, G., DENARO, L., DENARO, V., ROSSINI, L. & TOMBINI, M. 2012. In human implant of intraneural multielectrodes for controlling a 5-fingered hand prosthesis and delivering sensorial feedback. . *In:* PUBLISHERS, B. S. (ed.) *Grasping the Future: Advances in Powered Upper Limb Prosthetics.* Bentham Science Publisher.

DI PINO, G., MARAVITA, A., ZOLLO, L., GUGLIELMELLI, E. & DI LAZZARO, V. 2014. Augmentation-related brain plasticity. *Front Syst Neurosci,* 8**,** 109.

DOMINEY, P., DECETY, J., BROUSSOLLE, E., CHAZOT, G. & JEANNEROD, M. 1995. Motor imagery of a lateralized sequential task is asymmetrically slowed in hemi-Parkinson's patients. *Neuropsychologia,* 33**,** 727-41.

DRAGANSKI, B. & BHATIA, K. P. 2010. Brain structure in movement disorders: a neuroimaging perspective. *Curr Opin Neurol,* 23**,** 413-9.

DRAGANSKI, B., SCHNEIDER, S. A., FIORIO, M., KLOPPEL, S., GAMBARIN, M., TINAZZI, M., ASHBURNER, J., BHATIA, K. P. & FRACKOWIAK, R. S. 2009. Genotype-phenotype interactions in primary dystonias revealed by differential changes in brain structure. *Neuroimage,* 47**,** 1141-7.

DRAGOVIC, M. 2004. Towards an improved measure of the Edinburgh Handedness Inventory: a one-factor congeneric measurement model using confirmatory factor analysis. *Laterality,* 9**,** 411-9.

DRESEL, C., HASLINGER, B., CASTROP, F., WOHLSCHLAEGER, A. M. & CEBALLOS-BAUMANN, A. O. 2006. Silent event-related fMRI reveals deficient motor and enhanced somatosensory activation in orofacial dystonia. *Brain,* 129**,** 36-46.

EHRSSON, H. H., ROSEN, B., STOCKSELIUS, A., RAGNO, C., KOHLER, P. & LUNDBORG, G. 2008. Upper limb amputees can be induced to experience a rubber hand as their own. *Brain,* 131**,** 3443-52.

ESPAY, A. J., MORGANTE, F., PURZNER, J., GUNRAJ, C. A., LANG, A. E. & CHEN, R. 2006. Cortical and spinal abnormalities in psychogenic dystonia. *Ann Neurol,* 59**,** 825-34.

ETHIER, C., OBY, E. R., BAUMAN, M. J. & MILLER, L. E. 2012. Restoration of grasp following paralysis through brain-controlled stimulation of muscles. *Nature,* 485**,** 368-71.

EVANS, N. & BLANKE, O. 2013. Shared electrophysiology mechanisms of body ownership and motor imagery. *Neuroimage,* 64**,** 216-28.

FAHN, S., BRESSMAN, S. B. & MARSDEN, C. D. 1998. Classification of dystonia. *Adv Neurol,* 78**,** 1-10.

FAN, J. M., NUYUJUKIAN, P., KAO, J. C., CHESTEK, C. A., RYU, S. I. & SHENOY, K. V. 2014. Intention estimation in brain-machine interfaces. *J Neural Eng,* 11**,** 016004.

FAZLI, S., MEHNERT, J., STEINBRINK, J., CURIO, G., VILLRINGER, A., MULLER, K. R. & BLANKERTZ, B. 2012. Enhanced performance by a hybrid NIRS-EEG brain computer interface. *Neuroimage,* 59**,** 519-29.

FERREZ, P. & MILLÁN, J. D. R. 2005. You are wrong!—Automatic detection of interaction errors from brain waves.

FERREZ, P. W. & DEL, R. M. J. 2008. Error-related EEG potentials generated during simulated brain-computer interaction. *IEEE Trans Biomed Eng,* 55**,** 923-9.

FETZ, E. B. & FINOCCHI, D. V. 1971. Operant Conditioning of Specific Patterns of Neural and Muscular Activity. *Science,* 174**,** 431-&.

FETZ, E. E. 1969. Operant conditioning of cortical unit activity. *Science,* 163**,** 955-8.

FETZ, E. E. & BAKER, M. A. 1973. Operantly conditioned patterns on precentral unit activity and correlated responses in adjacent cells and contralateral muscles. *J Neurophysiol,* 36**,** 179-204.

FIORIO, M., GAMBARIN, M., VALENTE, E. M., LIBERINI, P., LOI, M., COSSU, G., MORETTO, G., BHATIA, K. P., DEFAZIO, G., AGLIOTI, S. M., FIASCHI, A. & TINAZZI, M. 2007a. Defective temporal processing of sensory stimuli in DYT1 mutation carriers: a new endophenotype of dystonia? *Brain,* 130**,** 134-42.

FIORIO, M., TINAZZI, M. & AGLIOTI, S. M. 2006. Selective impairment of hand mental rotation in patients with focal hand dystonia. *Brain,* 129**,** 47-54.

FIORIO, M., TINAZZI, M., BERTOLASI, L. & AGLIOTI, S. M. 2003. Temporal processing of visuotactile and tactile stimuli in writer's cramp. *Ann Neurol,* 53**,** 630-5.

FIORIO, M., TINAZZI, M., IONTA, S., FIASCHI, A., MORETTO, G., EDWARDS, M. J., BHATIA, K. P. & AGLIOTI, S. M. 2007b. Mental rotation of body parts and non-corporeal objects in patients with idiopathic cervical dystonia. *Neuropsychologia,* 45**,** 2346-54.

FIORIO, M., TINAZZI, M., SCONTRINI, A., STANZANI, C., GAMBARIN, M., FIASCHI, A., MORETTO, G., FABBRINI, G. & BERARDELLI, A. 2008. Tactile temporal discrimination in patients with blepharospasm. *J Neurol Neurosurg Psychiatry,* 79**,** 796-8.

FIORIO, M., WEISE, D., ONAL-HARTMANN, C., ZELLER, D., TINAZZI, M. & CLASSEN, J. 2011. Impairment of the rubber hand illusion in focal hand dystonia. *Brain,* 134**,** 1428-37.

FITZSIMMONS, N. A., DRAKE, W., HANSON, T. L., LEBEDEV, M. A. & NICOLELIS, M. A. 2007. Primate reaching cued by multichannel spatiotemporal cortical microstimulation. *J Neurosci,* 27**,** 5593-602.

FLANAGAN, J. R. & JOHANSSON, R. S. 2003. Action plans used in action observation. *Nature,* 424**,** 769-71.

FLINT, R. D., LINDBERG, E. W., JORDAN, L. R., MILLER, L. E. & SLUTZKY, M. W. 2012. Accurate decoding of reaching movements from field potentials in the absence of spikes. *J Neural Eng,* 9**,** 046006.

FOGASSI, L. & LUPPINO, G. 2005. Motor functions of the parietal lobe. *Curr Opin Neurobiol,* 15**,** 626-31.

FOURKAS, A. D., IONTA, S. & AGLIOTI, S. M. 2006. Influence of imagined posture and imagery modality on corticospinal excitability. *Behav Brain Res,* 168**,** 190-6.

FRANKLIN, D. W. & WOLPERT, D. M. 2011. Computational mechanisms of sensorimotor control. *Neuron,* 72**,** 425-42.

FUNK, M. & BRUGGER, P. 2008. Mental rotation of congenitally absent hands. *J Int Neuropsychol Soc,* 14**,** 81-9.

GALLAGHER, S. 2005. *How the Body Shapes the Mind,* Oxford, UK, Oxford University Press.

GANIS, G., KEENAN, J. P., KOSSLYN, S. M. & PASCUAL-LEONE, A. 2000. Transcranial magnetic stimulation of primary motor cortex affects mental rotation. *Cereb Cortex,* 10**,** 175-80.

GARRAUX, G., BAUER, A., HANAKAWA, T., WU, T., KANSAKU, K. & HALLETT, M. 2004. Changes in brain anatomy in focal hand dystonia. *Ann Neurol,* 55**,** 736-9.

GEORGOPOULOS, A. P. & MASSEY, J. T. 1987. Cognitive spatial-motor processes. 1. The making of movements at various angles from a stimulus direction. *Exp Brain Res,* 65**,** 361-70.

GHILARDI, M. F., CARBON, M., SILVESTRI, G., DHAWAN, V., TAGLIATI, M., BRESSMAN, S., GHEZ, C. & EIDELBERG, D. 2003. Impaired sequence learning in carriers of the DYT1 dystonia mutation. *Ann Neurol,* 54**,** 102-9.

GIETELING, E. W., VAN RIJN, M. A., DE JONG, B. M., HOOGDUIN, J. M., RENKEN, R., VAN HILTEN, J. J. & LEENDERS, K. L. 2008. Cerebral activation during motor imagery in complex regional pain syndrome type 1 with dystonia. *Pain,* 134**,** 302-9.

GLANNON, W. 2014. Neuromodulation, agency and autonomy. *Brain Topogr,* 27**,** 46-54.

GODDE, B., SPENGLER, F. & DINSE, H. R. 1996. Associative pairing of tactile stimulation induces somatosensory cortical reorganization in rats and humans. *Neuroreport,* 8**,** 281-5.

GRANERT, O., PELLER, M., GASER, C., GROPPA, S., HALLETT, M., KNUTZEN, A., DEUSCHL, G., ZEUNER, K. E. & SIEBNER, H. R. 2011a. Manual activity shapes structure and function in contralateral human motor hand area. *Neuroimage,* 54**,** 32-41.

GRANERT, O., PELLER, M., JABUSCH, H. C., ALTENMULLER, E. & SIEBNER, H. R. 2011b. Sensorimotor skills and focal dystonia are linked to putaminal grey-matter volume in pianists. *J Neurol Neurosurg Psychiatry,* 82**,** 1225-31.

GREZES, J. & DECETY, J. 2001. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. *Hum Brain Mapp,* 12**,** 1-19.

GRUNEWALD, R. A., YONEDA, Y., SHIPMAN, J. M. & SAGAR, H. J. 1997. Idiopathic focal dystonia: a disorder of muscle spindle afferent processing? *Brain,* 120 (Pt 12)**,** 2179-85.

GUGER, C., EDLINGER, G., HARKAM, W., NIEDERMAYER, I. & PFURTSCHELLER, G. 2003. How many people are able to operate an EEG-based brain-computer interface (BCI)? *IEEE Trans Neural Syst Rehabil Eng,* 11**,** 145-7.

HALLETT, M. 2006. Pathophysiology of dystonia. *J Neural Transm Suppl***,** 485-8.

HALLETT, M. 2007. Transcranial magnetic stimulation: a primer. *Neuron,* 55**,** 187-99.

HALLETT, M. 2011. Neurophysiology of dystonia: The role of inhibition. *Neurobiol Dis,* 42**,** 177-84.

HALLETT, M., BENECKE, R., BLITZER, A. & COMELLA, C. L. 2009. Treatment of focal dystonias with botulinum neurotoxin. *Toxicon,* 54**,** 628-33.

HALLETT, M., FIELDMAN, J., COHEN, L. G., SADATO, N. & PASCUAL-LEONE, A. 1994. Involvement of primary motor cortex in motor imagery and mental practice. *Behavioral and Brain Sciences,* 17**,** 210-210.

HAUSER, H., NEUMANN, G., IJSPEERT, A. J. & MAASS, W. 2011. Biologically inspired kinematic synergies enable linear balance control of a humanoid robot. *Biol Cybern,* 104**,** 235-49.

HAVRANKOVA, P., WALKER, N. D., OPERTO, G., SIEGER, T., VYMAZAL, J. & JECH, R. 2012. Cortical pattern of complex but not simple movements is affected in writer's cramp: a parametric event-related fMRI study. *Clin Neurophysiol,* 123**,** 755-63.

HELMICH, R. C., DE LANGE, F. P., BLOEM, B. R. & TONI, I. 2007. Cerebral compensation during motor imagery in Parkinson's disease. *Neuropsychologia,* 45**,** 2201-15.

HINKLEY, L. B., WEBSTER, R. L., BYL, N. N. & NAGARAJAN, S. S. 2009. Neuroimaging characteristics of patients with focal hand dystonia. *J Hand Ther,* 22**,** 125-34; quiz 135.

HOCHBERG, L. R., BACHER, D., JAROSIEWICZ, B., MASSE, N. Y., SIMERAL, J. D., VOGEL, J., HADDADIN, S., LIU, J., CASH, S. S., VAN DER SMAGT, P. & DONOGHUE, J. P. 2012. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature,* 485**,** 372-5.

HOCHBERG, L. R., SERRUYA, M. D., FRIEHS, G. M., MUKAND, J. A., SALEH, M., CAPLAN, A. H., BRANNER, A., CHEN, D., PENN, R. D. & DONOGHUE, J. P. 2006. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature,* 442**,** 164-71.

HU, X. Y., WANG, L., LIU, H. & ZHANG, S. Z. 2006. Functional magnetic resonance imaging study of writer's cramp. *Chin Med J (Engl),* 119**,** 1263-71.

HUBSCH, C., ROZE, E., POPA, T., RUSSO, M., BALACHANDRAN, A., PRADEEP, S., MUELLER, F., BROCHARD, V., QUARTARONE, A., DEGOS, B., VIDAILHET, M., KISHORE, A. & MEUNIER, S. 2013. Defective cerebellar control of cortical plasticity in writer's cramp. *Brain,* 136**,** 2050-62.

HWANG, H. J., LIM, J. H., JUNG, Y. J., CHOI, H., LEE, S. W. & IM, C. H. 2012. Development of an SSVEP-based BCI spelling system adopting a QWERTY-style LED keyboard. *J Neurosci Methods,* 208**,** 59-65.

IACOBONI, M., WOODS, R. P., BRASS, M., BEKKERING, H., MAZZIOTTA, J. C. & RIZZOLATTI, G. 1999. Cortical mechanisms of human imitation. *Science,* 286**,** 2526-8.

IBANEZ, V., SADATO, N., KARP, B., DEIBER, M. P. & HALLETT, M. 1999. Deficient activation of the motor cortical network in patients with writer's cramp. *Neurology,* 53**,** 96-105.

IJSPEERT, A. J. 2008. Central pattern generators for locomotion control in animals and robots: a review. *Neural Netw,* 21**,** 642-53.

IONTA, S. & BLANKE, O. 2009. Differential influence of hands posture on mental rotation of hands and feet in left and right handers. *Exp Brain Res,* 195**,** 207-17.

IONTA, S., FERRETTI, A., MERLA, A., TARTARO, A. & ROMANI, G. L. 2010a. Step-by-step: the effects of physical practice on the neural correlates of locomotion imagery revealed by fMRI. *Hum Brain Mapp,* 31**,** 694-702.

IONTA, S., FOURKAS, A. D. & AGLIOTI, S. M. 2010b. Egocentric and object-based transformations in the laterality judgement of human and animal faces and of non-corporeal objects. *Behav Brain Res,* 207**,** 452-7.

IONTA, S., FOURKAS, A. D., FIORIO, M. & AGLIOTI, S. M. 2007. The influence of hands posture on mental rotation of hands and feet. *Exp Brain Res,* 183**,** 1-7.

IONTA, S., PERRUCHOUD, D., DRAGANSKI, B. & BLANKE, O. 2012. Body context and posture affect mental imagery of hands. *PLoS One,* 7**,** e34382.

IONTA, S., SFORZA, A., FUNATO, M. & BLANKE, O. 2013. Anatomically plausible illusory posture affects mental rotation of body parts. *Cogn Affect Behav Neurosci,* 13**,** 197-209.

ISLAM, T., KUPSCH, A., BRUHN, H., SCHEURIG, C., SCHMIDT, S. & HOFFMANN, K. T. 2009. Decreased bilateral cortical representation patterns in writer's cramp: a functional magnetic resonance imaging study at 3.0 T. *Neurol Sci,* 30**,** 219-26.

JACKSON, A. B., DIJKERS, M., DEVIVO, M. J. & POCZATEK, R. B. 2004. A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years. *Arch Phys Med Rehabil,* 85**,** 1740-8.

JANKOVIC, J. 2009. Treatment of hyperkinetic movement disorders. *Lancet Neurol,* 8**,** 844-56.

JANKOWSKI, J., PAUS, S., SCHEEF, L., BEWERSDORFF, M., SCHILD, H. H., KLOCKGETHER, T. & BOECKER, H. 2013. Abnormal movement preparation in task-specific focal hand dystonia. *PLoS One,* 8**,** e78234.

JEANNEROD, M. 1995. Mental imagery in the motor context. *Neuropsychologia,* 33**,** 1419-32.

JEANNEROD, M. 2001. Neural simulation of action: a unifying mechanism for motor cognition. *Neuroimage,* 14**,** S103-9.

JEANNEROD, M. & DECETY, J. 1995. Mental motor imagery: a window into the representational stages of action. *Curr Opin Neurobiol,* 5**,** 727-32.

JOHANSSON, R. S. & FLANAGAN, J. R. 2009. Coding and use of tactile signals from the fingertips in object manipulation tasks. *Nat Rev Neurosci,* 10**,** 345-59.

JOHANSSON, R. S., WESTLING, G., BACKSTROM, A. & FLANAGAN, J. R. 2001. Eye-hand coordination in object manipulation. *J Neurosci,* 21**,** 6917-32.

JOHNSON, S. H. 1998. Cerebral organization of motor imagery: contralateral control of grip selection in mentally represented prehension. *Psychological Science,* 9**,** 219-222.

KADOTA, H., NAKAJIMA, Y., MIYAZAKI, M., SEKIGUCHI, H., KOHNO, Y., AMAKO, M., ARINO, H., NEMOTO, K. & SAKAI, N. 2010. An fMRI study of musicians with focal dystonia during tapping tasks. *J Neurol,* 257**,** 1092-8.

KATSCHNIG, P., EDWARDS, M. J., SCHWINGENSCHUH, P., AGUIRREGOMOZCORTA, M., KAGI, G., ROTHWELL, J. C. & BHATIA, K. P. 2010. Mental rotation of body parts and sensory temporal discrimination in fixed dystonia. *Mov Disord,* 25**,** 1061-7.

KAWAMICHI, H., KIKUCHI, Y., ENDO, H., TAKEDA, T. & YOSHIZAWA, S. 1998. Temporal structure of implicit motor imagery in visual hand-shape discrimination as revealed by MEG. *Neuroreport,* 9**,** 1127-32.

KIM, J., LEE, M., SHIM, H. J., GHAFFARI, R., CHO, H. R., SON, D., JUNG, Y. H., SOH, M., CHOI, C., JUNG, S., CHU, K., JEON, D., LEE, S. T., KIM, J. H., CHOI, S. H., HYEON, T. & KIM, D. H. 2014. Stretchable silicon nanoribbon electronics for skin prosthesis. *Nat Commun,* 5**,** 5747.

KIM, K. & COLGATE, J. E. 2012. Haptic feedback enhances grip force control of sEMG-controlled prosthetic hands in targeted reinnervation amputees. *IEEE Trans Neural Syst Rehabil Eng,* 20**,** 798-805.

KIMBERLEY, T. J., BORICH, M. R., PROCHASKA, K. D., MUNDFROM, S. L., PERKINS, A. E. & POEPPING, J. M. 2009. Establishing the definition and inter-rater reliability of cortical silent period

calculation in subjects with focal hand dystonia and healthy controls. *Neurosci Lett,* 464**,** 84-7.

KNECHT, S., HENNINGSEN, H., ELBERT, T., FLOR, H., HOHLING, C., PANTEV, C. & TAUB, E. 1996. Reorganizational and perceptional changes after amputation. *Brain,* 119 (Pt 4)**,** 1213-9.

KOSSLYN, S. M., DIGIROLAMO, G. J., THOMPSON, W. L. & ALPERT, N. M. 1998. Mental rotation of objects versus hands: neural mechanisms revealed by positron emission tomography. *Psychophysiology,* 35**,** 151-61.

KOSSLYN, S. M., GANIS, G. & THOMPSON, W. L. 2001a. Neural foundations of imagery. *Nat Rev Neurosci,* 2**,** 635-42.

KOSSLYN, S. M., THOMPSON, W. L., WRAGA, M. & ALPERT, N. M. 2001b. Imagining rotation by endogenous versus exogenous forces: distinct neural mechanisms. *Neuroreport,* 12**,** 2519-25.

KRYSTKOWIAK, P., MARTINAT, P., DEFEBVRE, L., PRUVO, J. P., LEYS, D. & DESTEE, A. 1998. Dystonia after striatopallidal and thalamic stroke: clinicoradiological correlations and pathophysiological mechanisms. *J Neurol Neurosurg Psychiatry,* 65**,** 703-8.

KUHTZ-BUSCHBECK, J. P., MAHNKOPF, C., HOLZKNECHT, C., SIEBNER, H., ULMER, S. & JANSEN, O. 2003. Effector-independent representations of simple and complex imagined finger movements: a combined fMRI and TMS study. *Eur J Neurosci,* 18**,** 3375-87.

KUIKEN, T. A., DUMANIAN, G., LIPSCHUTZ, R., MILLER, L. & STUBBLEFIELD, K. 2004. The use of targeted muscle reinnervation for improved myoelectric prosthesis control in a bilateral shoulder disarticulation amputee. *Prosthetics and Orthotics International,* 28**,** 245-253.

KUIKEN, T. A., LI, G., LOCK, B. A., LIPSCHUTZ, R. D., MILLER, L. A., STUBBLEFIELD, K. A. & ENGLEHART, K. B. 2009. Targeted muscle reinnervation for real-time myoelectric control of multifunction artificial arms. *JAMA,* 301**,** 619-28.

KUIKEN, T. A., MARASCO, P. D., LOCK, B. A., HARDEN, R. N. & DEWALD, J. P. 2007. Redirection of cutaneous sensation from the hand to the chest skin of human amputees with targeted reinnervation. *Proc Natl Acad Sci U S A,* 104**,** 20061-6.

LACOURSE, M. G., ORR, E. L., CRAMER, S. C. & COHEN, M. J. 2005. Brain activation during execution and motor imagery of novel and skilled sequential hand movements. *Neuroimage,* 27**,** 505-19.

LACRUZ, F., ARTIEDA, J., PASTOR, M. A. & OBESO, J. A. 1991. The anatomical basis of somaesthetic temporal discrimination in humans. *J Neurol Neurosurg Psychiatry,* 54**,** 1077-81.

LAL, S. K., CRAIG, A., BOORD, P., KIRKUP, L. & NGUYEN, H. 2003. Development of an algorithm for an EEG-based driver fatigue countermeasure. *J Safety Res,* 34**,** 321-8.

LEBEDEV, M. A., DENTON, J. M. & NELSON, R. J. 1994. Vibration-entrained and premovement activity in monkey primary somatosensory cortex. *J Neurophysiol,* 72**,** 1654-73.

LEBEDEV, M. A. & NICOLELIS, M. A. L. 2006. Brain-machine interfaces: past, present and future. *Trends in Neurosciences,* 29**,** 536-546.

LEBON, F., LOTZE, M., STINEAR, C. M. & BYBLOW, W. D. 2012. Task-dependent interaction between parietal and contralateral primary motor cortex during explicit versus implicit motor imagery. *PLoS One,* 7**,** e37850.

LEHERICY, S., GERARDIN, E., POLINE, J. B., MEUNIER, S., VAN DE MOORTELE, P. F., LE BIHAN, D. & VIDAILHET, M. 2004. Motor execution and imagination networks in post-stroke dystonia. *Neuroreport,* 15**,** 1887-90.

LENAY, C., GAPENNE, O., HANNETON, S., MARQUE, C. & GENOUËLLE, C. 2003. Sensory substitution: limits and perspectives. *Touching for knowing*, 275-292.

LEUTHARDT, E. C., GAONA, C., SHARMA, M., SZRAMA, N., ROLAND, J., FREUDENBERG, Z., SOLIS, J., BRESHEARS, J. & SCHALK, G. 2011. Using the electrocorticographic speech network to control a brain-computer interface in humans. *J Neural Eng,* 8**,** 036004.

LEUTHARDT, E. C., SCHALK, G., WOLPAW, J. R., OJEMANN, J. G. & MORAN, D. W. 2004. A brain-computer interface using electrocorticographic signals in humans. *J Neural Eng,* 1**,** 63-71.

LIEPERT, J., HASSA, T., TUSCHER, O. & SCHMIDT, R. 2011. Motor excitability during movement imagination and movement observation in psychogenic lower limb paresis. *J Psychosom Res,* 70**,** 59-65.

LIN, P. T. & HALLETT, M. 2009. The pathophysiology of focal hand dystonia. *J Hand Ther,* 22**,** 109-13; quiz 114.

LIU, Y., DENTON, J. M. & NELSON, R. J. 2005. Neuronal activity in primary motor cortex differs when monkeys perform somatosensory and visually guided wrist movements. *Exp Brain Res,* 167**,** 571-86.

MAK, J. N. & WOLPAW, J. R. 2009. Clinical Applications of Brain-Computer Interfaces: Current State and Future Prospects. *IEEE Rev Biomed Eng,* 2**,** 187-199.

MARASCO, P. D., KIM, K., COLGATE, J. E., PESHKIN, M. A. & KUIKEN, T. A. 2011. Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees. *Brain,* 134**,** 747-58.

MARASCO, P. D., SCHULTZ, A. E. & KUIKEN, T. A. 2009. Sensory capacity of reinnervated skin after redirection of amputated upper limb nerves to the chest. *Brain,* 132**,** 1441-8.

MARIN, C. & FERNANDEZ, E. 2010. Biocompatibility of intracortical microelectrodes: current status and future prospects. *Front Neuroeng,* 3**,** 8.

MARQUEZ-CHIN, C., POPOVIC, M. R., CAMERON, T., LOZANO, A. M. & CHEN, R. 2009. Control of a neuroprosthesis for grasping using off-line classification of electrocorticographic signals: case study. *Spinal Cord,* 47**,** 802-808.

MATSUMURA, M., SAWAGUCHI, T. & KUBOTA, K. 1992. GABAergic inhibition of neuronal activity in the primate motor and premotor cortex during voluntary movement. *J Neurophysiol,* 68**,** 692-702.

MATSUMURA, M., SAWAGUCHI, T., OISHI, T., UEKI, K. & KUBOTA, K. 1991. Behavioral deficits induced by local injection of bicuculline and muscimol into the primate motor and premotor cortex. *J Neurophysiol,* 65**,** 1542-53.

MATTOUT, J., PERRIN, M., BERTRAND, O. & MABY, E. 2015. Improving BCI performance through co-adaptation: applications to the P300-speller. *Ann Phys Rehabil Med,* 58**,** 23-8.

MCFARLAND, D. J., SARNACKI, W. A. & WOLPAW, J. R. 2010. Electroencephalographic (EEG) control of three-dimensional movement. *J Neural Eng,* 7**,** 036007.

MCNORGAN, C. 2012. A meta-analytic review of multisensory imagery identifies the neural correlates of modality-specific and modality-general imagery. *Front Hum Neurosci,* 6**,** 285.

MELLINGER, J., SCHALK, G., BRAUN, C., PREISSL, H., ROSENSTIEL, W., BIRBAUMER, N. & KUBLER, A. 2007. An MEG-based brain-computer interface (BCI). *Neuroimage,* 36**,** 581-93.

MEMBERG, W. D., POLASEK, K. H., HART, R. L., BRYDEN, A. M., KILGORE, K. L., NEMUNAITIS, G. A., HOYEN, H. A., KEITH, M. W. & KIRSCH, R. F. 2014. Implanted neuroprosthesis for restoring

arm and hand function in people with high level tetraplegia. *Arch Phys Med Rehabil,* 95**,** 1201-1211 e1.

MICERA, S., CARPANETO, J. & RASPOPOVIC, S. 2010a. Control of hand prostheses using peripheral information. *IEEE Rev Biomed Eng,* 3**,** 48-68.

MICERA, S., CITI, L., RIGOSA, J., CARPANETO, J., RASPOPOVIC, S., DI PINO, G., ROSSINI, L., YOSHIDA, K., DENARO, L. & DARIO, P. 2010b. Decoding information from neural signals recorded using intraneural electrodes: toward the development of a neurocontrolled hand prosthesis. *Proceedings of the IEEE,* 98**,** 407-417.

MICERA, S., ROSSINI, P. M., RIGOSA, J., CITI, L., CARPANETO, J., RASPOPOVIC, S., TOMBINI, M., CIPRIANI, C., ASSENZA, G., CARROZZA, M. C., HOFFMANN, K. P., YOSHIDA, K., NAVARRO, X. & DARIO, P. 2011. Decoding of grasping information from neural signals recorded using peripheral intrafascicular interfaces. *J Neuroeng Rehabil,* 8**,** 53.

MILEKOVIC, T., FISCHER, J., PISTOHL, T., RUESCHER, J., SCHULZE-BONHAGE, A., AERTSEN, A., RICKERT, J., BALL, T. & MEHRING, C. 2012. An online brain-machine interface using decoding of movement direction from the human electrocorticogram. *J Neural Eng,* 9**,** 046003.

MILLÁN, J. D., RUPP, R., MULLER-PUTZ, G. R., MURRAY-SMITH, R., GIUGLIEMMA, C., TANGERMANN, M., VIDAURRE, C., CINCOTTI, F., KUBLER, A., LEEB, R., NEUPER, C., MULLER, K. R. & MATTIA, D. 2010. Combining Brain-Computer Interfaces and Assistive Technologies: State-of-the-Art and Challenges. *Front Neurosci,* 4.

MINIUSSI, C. & THUT, G. 2010. Combining TMS and EEG offers new prospects in cognitive neuroscience. *Brain Topogr,* 22**,** 249-56.

MOHAMMADI, B., KOLLEWE, K., SAMII, A., BECKMANN, C. F., DENGLER, R. & MUNTE, T. F. 2012. Changes in resting-state brain networks in writer's cramp. *Hum Brain Mapp,* 33**,** 840-8.

MOLLOY, F. M., CARR, T. D., ZEUNER, K. E., DAMBROSIA, J. M. & HALLETT, M. 2003. Abnormalities of spatial discrimination in focal and generalized dystonia. *Brain,* 126**,** 2175-82.

MOORE, R. D., GALLEA, C., HOROVITZ, S. G. & HALLETT, M. 2012. Individuated finger control in focal hand dystonia: an fMRI study. *Neuroimage,* 61**,** 823-31.

MUNZERT, J., LOREY, B. & ZENTGRAF, K. 2009. Cognitive motor processes: the role of motor imagery in the study of motor representations. *Brain Res Rev,* 60**,** 306-26.

MURASE, N., KAJI, R., SHIMAZU, H., KATAYAMA-HIROTA, M., IKEDA, A., KOHARA, N., KIMURA, J., SHIBASAKI, H. & ROTHWELL, J. C. 2000. Abnormal premovement gating of somatosensory input in writer's cramp. *Brain,* 123 (Pt 9)**,** 1813-29.

NAKASHIMA, K., ROTHWELL, J. C., DAY, B. L., THOMPSON, P. D., SHANNON, K. & MARSDEN, C. D. 1989. Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. *Brain,* 112 (Pt 3)**,** 681-97.

NICO, D., DAPRATI, E., RIGAL, F., PARSONS, L. & SIRIGU, A. 2004. Left and right hand recognition in upper limb amputees. *Brain,* 127**,** 120-32.

NICOLELIS, M. & SERVICK, K. 2014. Interview. Kickoff looms for demo of brain-controlled machine. *Science,* 344**,** 1069-70.

NICOLELIS, M. A. 2012. Mind in motion. *Sci Am,* 307**,** 58-63.

O'CONNOR, D. H., HIRES, S. A., GUO, Z. V., LI, N., YU, J., SUN, Q. Q., HUBER, D. & SVOBODA, K. 2013. Neural coding during active somatosensation revealed using illusory touch. *Nat Neurosci,* 16**,** 958-65.

O'DOHERTY, J. E., LEBEDEV, M. A., HANSON, T. L., FITZSIMMONS, N. A. & NICOLELIS, M. A. 2009. A brain-machine interface instructed by direct intracortical microstimulation. *Front Integr Neurosci,* 3**,** 20.

O'DOHERTY, J. E., LEBEDEV, M. A., LI, Z. & NICOLELIS, M. A. L. 2012. Virtual Active Touch Using Randomly Patterned Intracortical Microstimulation. *Ieee Transactions on Neural Systems and Rehabilitation Engineering,* 20**,** 85-93.

O'REILLY, J. X., JBABDI, S., RUSHWORTH, M. F. & BEHRENS, T. E. 2013. Brain systems for probabilistic and dynamic prediction: computational specificity and integration. *PLoS Biol,* 11**,** e1001662.

OGA, T., HONDA, M., TOMA, K., MURASE, N., OKADA, T., HANAKAWA, T., SAWAMOTO, N., NAGAMINE, T., KONISHI, J., FUKUYAMA, H., KAJI, R. & SHIBASAKI, H. 2002. Abnormal cortical mechanisms of voluntary muscle relaxation in patients with writer's cramp: an fMRI study. *Brain,* 125**,** 895-903.

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

PANIZZA, M., LELLI, S., NILSSON, J. & HALLETT, M. 1990. H-reflex recovery curve and reciprocal inhibition of H-reflex in different kinds of dystonia. *Neurology,* 40**,** 824-8.

PAPADELIS, C., KOURTIDOU-PAPADELI, C., BAMIDIS, P. & ALBANI, M. 2007. Effects of imagery training on cognitive performance and use of physiological measures as an assessment tool of mental effort. *Brain Cogn,* 64**,** 74-85.

PARSONS, L. M. 1987. Imagined spatial transformation of one's body. *J Exp Psychol Gen,* 116**,** 172-91.

PARSONS, L. M. 1994. Temporal and kinematic properties of motor behavior reflected in mentally simulated action. *J Exp Psychol Hum Percept Perform,* 20**,** 709-30.

PARSONS, L. M. 2001. Integrating cognitive psychology, neurology and neuroimaging. *Acta Psychol (Amst),* 107**,** 155-81.

PARSONS, L. M., FOX, P. T., DOWNS, J. H., GLASS, T., HIRSCH, T. B., MARTIN, C. C., JERABEK, P. A. & LANCASTER, J. L. 1995. Use of implicit motor imagery for visual shape discrimination as revealed by PET.

PELGRIMS, B., MICHAUX, N., OLIVIER, E. & ANDRES, M. 2011. Contribution of the primary motor cortex to motor imagery: a subthreshold TMS study. *Hum Brain Mapp,* 32**,** 1471-82.

PELLER, M., ZEUNER, K. E., MUNCHAU, A., QUARTARONE, A., WEISS, M., KNUTZEN, A., HALLETT, M., DEUSCHL, G. & SIEBNER, H. R. 2006. The basal ganglia are hyperactive during the discrimination of tactile stimuli in writer's cramp. *Brain,* 129**,** 2697-708.

PEREZ-MARCOS, D., SLATER, M. & SANCHEZ-VIVES, M. V. 2009. Inducing a virtual hand ownership illusion through a brain-computer interface. *Neuroreport,* 20**,** 589-94.

PEREZ, M. A. & COHEN, L. G. 2009. Interhemispheric inhibition between primary motor cortices: what have we learned? *J Physiol,* 587**,** 725-6.

PERRUCHOUD, D., MICHELS, L., PICCIRELLI, M., GASSERT, R. & IONTA, S. 2016. Differential neural encoding of sensorimotor and visual body representations. *Sci Rep,* 6**,** 37259.

PERRUCHOUD, D., MURRAY, M. M., LEFEBVRE, J. & IONTA, S. 2014. Focal dystonia and the Sensory-Motor Integrative Loop for Enacting (SMILE). *Front Hum Neurosci,* 8**,** 458.

PETERKA, R. J. 2002. Sensorimotor integration in human postural control. *J Neurophysiol,* 88**,** 1097-118.

PISOTTA, I. & MOLINARI, M. 2014. Cerebellar contribution to feedforward control of locomotion. *Front Hum Neurosci,* 8**,** 475.

PISOTTA, I., PERRUCHOUD, D. & IONTA, S. 2015. Hand-in-hand advances in biomedical engineering and sensorimotor restoration. *J Neurosci Methods,* 246**,** 22-29.

PISTOHL, T., SCHULZE-BONHAGE, A., AERTSEN, A., MEHRING, C. & BALL, T. 2012. Decoding natural grasp types from human ECoG. *Neuroimage,* 59**,** 248-60.

PIZZOLATO, F., FIORIO, M. & CESARI, P. 2012. Motor system modulation for movement direction and rotation angle during motor imagery. *Neuroscience,* 218**,** 154-60.

PLAYFORD, E. D., PASSINGHAM, R. E., MARSDEN, C. D. & BROOKS, D. J. 1998. Increased activation of frontal areas during arm movement in idiopathic torsion dystonia. *Mov Disord,* 13**,** 309-18.

POLIKOV, V. S., TRESCO, P. A. & REICHERT, W. M. 2005. Response of brain tissue to chronically implanted neural electrodes. *J Neurosci Methods,* 148**,** 1-18.

POWER, S. D., KUSHKI, A. & CHAU, T. 2011. Towards a system-paced near-infrared spectroscopy brain-computer interface: differentiating prefrontal activity due to mental arithmetic and mental singing from the no-control state. *J Neural Eng,* 8**,** 066004.

PREIBISCH, C., BERG, D., HOFMANN, E., SOLYMOSI, L. & NAUMANN, M. 2001. Cerebral activation patterns in patients with writer's cramp: a functional magnetic resonance imaging study. *J Neurol,* 248**,** 10-7.

PRESACCO, A., GOODMAN, R., FORRESTER, L. & CONTRERAS-VIDAL, J. L. 2011. Neural decoding of treadmill walking from noninvasive electroencephalographic signals. *J Neurophysiol,* 106**,** 1875-87.

PUJOL, J., ROSET-LLOBET, J., ROSINES-CUBELLS, D., DEUS, J., NARBERHAUS, B., VALLS-SOLE, J., CAPDEVILA, A. & PASCUAL-LEONE, A. 2000. Brain cortical activation during guitar-induced hand dystonia studied by functional MRI. *Neuroimage,* 12**,** 257-67.

QUANDT, F., REICHERT, C., HINRICHS, H., HEINZE, H. J., KNIGHT, R. T. & RIEGER, J. W. 2012. Single trial discrimination of individual finger movements on one hand: a combined MEG and EEG study. *Neuroimage,* 59**,** 3316-24.

QUARTARONE, A. & PISANI, A. 2011. Abnormal plasticity in dystonia: Disruption of synaptic homeostasis. *Neurobiol Dis,* 42**,** 162-70.

QUARTARONE, A., RIZZO, V. & MORGANTE, F. 2008. Clinical features of dystonia: a pathophysiological revisitation. *Curr Opin Neurol,* 21**,** 484-90.

QUARTARONE, A., SIEBNER, H. R. & ROTHWELL, J. C. 2006. Task-specific hand dystonia: can too much plasticity be bad for you? *Trends Neurosci,* 29**,** 192-9.

R DEVELOPMENT CORE TEAM 2014. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2014. R Foundation for Statistical Computing.

RAIKE, R. S., PIZOLI, C. E., WEISZ, C., VAN DEN MAAGDENBERG, A. M., JINNAH, H. A. & HESS, E. J. 2012. Limited regional cerebellar dysfunction induces focal dystonia in mice. *Neurobiol Dis,* 49C**,** 200-210.

RAMACHANDRAN, V. S. & ALTSCHULER, E. L. 2009. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. *Brain,* 132**,** 1693-710.

RAMOS-MURGUIALDAY, A., SCHURHOLZ, M., CAGGIANO, V., WILDGRUBER, M., CARIA, A., HAMMER, E. M., HALDER, S. & BIRBAUMER, N. 2012. Proprioceptive feedback and brain computer interface (BCI) based neuroprostheses. *PLoS One,* 7**,** e47048.

RASPOPOVIC, S., CAPOGROSSO, M., PETRINI, F. M., BONIZZATO, M., RIGOSA, J., DI PINO, G., CARPANETO, J., CONTROZZI, M., BORETIUS, T., FERNANDEZ, E., GRANATA, G., ODDO, C. M.,

CITI, L., CIANCIO, A. L., CIPRIANI, C., CARROZZA, M. C., JENSEN, W., GUGLIELMELLI, E., STIEGLITZ, T., ROSSINI, P. M. & MICERA, S. 2014. Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Sci Transl Med,* 6**,** 222ra19.

RIDDING, M. C., SHEEAN, G., ROTHWELL, J. C., INZELBERG, R. & KUJIRAI, T. 1995. Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. *J Neurol Neurosurg Psychiatry,* 59**,** 493-8.

ROHDE, M., DI LUCA, M. & ERNST, M. O. 2011. The Rubber Hand Illusion: feeling of ownership and proprioceptive drift do not go hand in hand. *PLoS One,* 6**,** e21659.

ROMO, R., HERNANDEZ, A., ZAINOS, A. & SALINAS, E. 1998. Somatosensory discrimination based on cortical microstimulation. *Nature,* 392**,** 387-90.

ROSEN, B., EHRSSON, H. H., ANTFOLK, C., CIPRIANI, C., SEBELIUS, F. & LUNDBORG, G. 2009. Referral of sensation to an advanced humanoid robotic hand prosthesis. *Scand J Plast Reconstr Surg Hand Surg,* 43**,** 260-6.

ROSENKRANZ, K., ALTENMULLER, E., SIGGELKOW, S. & DENGLER, R. 2000. Alteration of sensorimotor integration in musician's cramp: impaired focusing of proprioception. *Clin Neurophysiol,* 111**,** 2040-5.

ROSSINI, P. M., MICERA, S., BENVENUTO, A., CARPANETO, J., CAVALLO, G., CITI, L., CIPRIANI, C., DENARO, L., DENARO, V., DI PINO, G., FERRERI, F., GUGLIELMELLI, E., HOFFMANN, K. P., RASPOPOVIC, S., RIGOSA, J., ROSSINI, L., TOMBINI, M. & DARIO, P. 2010. Double nerve intraneural interface implant on a human amputee for robotic hand control. *Clin Neurophysiol,* 121**,** 777-83.

ROTHWELL, J. C. & HUANG, Y. Z. 2003. Systems-level studies of movement disorders in dystonia and Parkinson's disease. *Curr Opin Neurobiol,* 13**,** 691-5.

ROZE, E., SOUMARE, A., PIRONNEAU, I., SANGLA, S., DE COCK, V. C., TEIXEIRA, A., ASTORQUIZA, A., BONNET, C., BLETON, J. P., VIDAILHET, M. & ELBAZ, A. 2009. Case-control study of writer's cramp. *Brain,* 132**,** 756-64.

RUIZ, S., BUYUKTURKOGLU, K., RANA, M., BIRBAUMER, N. & SITARAM, R. 2014. Real-time fMRI brain computer interfaces: self-regulation of single brain regions to networks. *Biol Psychol,* 95**,** 4-20.

RUPP, R., KLEIH, S. C., LEEB, R., MILLÁN, J. D. R., KÜBLER, A. & MÜLLER-PUTZ, G. R. 2014. Brain–Computer Interfaces and Assistive Technology. *Brain-Computer-Interfaces in their ethical, social and cultural contexts.* Springer.

SAAL, H. P. & BENSMAIA, S. J. 2014. Touch is a team effort: interplay of submodalities in cutaneous sensibility. *Trends Neurosci*.

SAINBURG, R. L. 2002. Evidence for a dynamic-dominance hypothesis of handedness. *Exp Brain Res,* 142**,** 241-58.

SAINBURG, R. L., GHILARDI, M. F., POIZNER, H. & GHEZ, C. 1995. Control of limb dynamics in normal subjects and patients without proprioception. *J Neurophysiol,* 73**,** 820-35.

SAISANEN, L., JULKUNEN, P., NISKANEN, E., DANNER, N., HUKKANEN, T., LOHIOJA, T., NURKKALA, J., MERVAALA, E., KARHU, J. & KONONEN, M. 2008. Motor potentials evoked by navigated transcranial magnetic stimulation in healthy subjects. *J Clin Neurophysiol,* 25**,** 367-72.

SAMUEL, M., CEBALLOS-BAUMANN, A. O., BOECKER, H. & BROOKS, D. J. 2001. Motor imagery in normal subjects and Parkinson's disease patients: an H215O PET study. *Neuroreport,* 12**,** 821-8.

SANGER, T. D. & MERZENICH, M. M. 2000. Computational model of the role of sensory disorganization in focal task-specific dystonia. *J Neurophysiol,* 84**,** 2458-64.

SANGER, T. D., TARSY, D. & PASCUAL-LEONE, A. 2001. Abnormalities of spatial and temporal sensory discrimination in writer's cramp. *Mov Disord,* 16**,** 94-9.

SANTO DI NUOVO, V. D. L., CRUZ, D. C., BUONO, S. & DI NUOVO, A. 2014. Mental Imagery: rehabilitation through simulation.

SATTLER, V., DICKLER, M., MICHAUD, M., MEUNIER, S. & SIMONETTA-MOREAU, M. 2013. Does abnormal interhemispheric inhibition play a role in mirror dystonia? *Mov Disord*.

SAUNER, D., BESTMANN, S., SIEBNER, H. R. & ROTHWELL, J. C. 2006. No evidence for a substantial involvement of primary motor hand area in handedness judgements: a transcranial magnetic stimulation study. *Eur J Neurosci,* 23**,** 2215-24.

SCHAEFER, S. Y., HAALAND, K. Y. & SAINBURG, R. L. 2007. Ipsilesional motor deficits following stroke reflect hemispheric specializations for movement control. *Brain,* 130**,** 2146-58.

SCHALK, G., MILLER, K. J., ANDERSON, N. R., WILSON, J. A., SMYTH, M. D., OJEMANN, J. G., MORAN, D. W., WOLPAW, J. R. & LEUTHARDT, E. C. 2008. Two-dimensional movement control using electrocorticographic signals in humans. *J Neural Eng,* 5**,** 75-84.

SCHEME, E. & ENGLEHART, K. 2011. Electromyogram pattern recognition for control of powered upper-limb prostheses: state of the art and challenges for clinical use. *J Rehabil Res Dev,* 48**,** 643-59.

SCHNEIDER, S. A., PLEGER, B., DRAGANSKI, B., CORDIVARI, C., ROTHWELL, J. C., BHATIA, K. P. & DOLAN, R. J. 2010. Modulatory effects of 5Hz rTMS over the primary somatosensory cortex in focal dystonia--an fMRI-TMS study. *Mov Disord,* 25**,** 76-83.

SCHNITZLER, A. & GROSS, J. 2005. Normal and pathological oscillatory communication in the brain. *Nat Rev Neurosci,* 6**,** 285-96.

SCONTRINI, A., CONTE, A., DEFAZIO, G., FIORIO, M., FABBRINI, G., SUPPA, A., TINAZZI, M. & BERARDELLI, A. 2009. Somatosensory temporal discrimination in patients with primary focal dystonia. *J Neurol Neurosurg Psychiatry,* 80**,** 1315-9.

SELLERS, E. W., VAUGHAN, T. M. & WOLPAW, J. R. 2010. A brain-computer interface for long-term independent home use. *Amyotroph Lateral Scler,* 11**,** 449-55.

SENSINGER, J. W., SCHULTZ, A. E. & KUIKEN, T. A. 2009. Examination of force discrimination in human upper limb amputees with reinnervated limb sensation following peripheral nerve transfer. *IEEE Trans Neural Syst Rehabil Eng,* 17**,** 438-44.

SERRUYA, M. D., HATSOPOULOS, N. G., PANINSKI, L., FELLOWS, M. R. & DONOGHUE, J. P. 2002. Instant neural control of a movement signal. *Nature,* 416**,** 141-2.

SHADMEHR, R. & KRAKAUER, J. W. 2008. A computational neuroanatomy for motor control. *Experimental brain research. Experimentelle Hirnforschung. Experimentation cerebrale,* 185**,** 359-81.

SIEBNER, H. R., FILIPOVIC, S. R., ROWE, J. B., CORDIVARI, C., GERSCHLAGER, W., ROTHWELL, J. C., FRACKOWIAK, R. S. & BHATIA, K. P. 2003. Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. *Brain,* 126**,** 2710-25.

SIMERAL, J. D., KIM, S. P., BLACK, M. J., DONOGHUE, J. P. & HOCHBERG, L. R. 2011. Neural control of cursor trajectory and click by a human with tetraplegia 1000 days after implant of an intracortical microelectrode array. *J Neural Eng,* 8**,** 025027.

SIRIGU, A., DUHAMEL, J. R., COHEN, L., PILLON, B., DUBOIS, B. & AGID, Y. 1996. The mental representation of hand movements after parietal cortex damage. *Science,* 273**,** 1564-8.

SITARAM, R., ZHANG, H., GUAN, C., THULASIDAS, M., HOSHI, Y., ISHIKAWA, A., SHIMIZU, K. & BIRBAUMER, N. 2007. Temporal classification of multichannel near-infrared spectroscopy signals of motor imagery for developing a brain-computer interface. *Neuroimage,* 34**,** 1416-27.

SKEDUNG, L., ARVIDSSON, M., CHUNG, J. Y., STAFFORD, C. M., BERGLUND, B. & RUTLAND, M. W. 2013. Feeling small: exploring the tactile perception limits. *Sci Rep,* 3**,** 2617.

SNIJDERS, A. H., LEUNISSEN, I., BAKKER, M., OVEREEM, S., HELMICH, R. C., BLOEM, B. R. & TONI, I. 2011. Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. *Brain,* 134**,** 59-72.

SOHN, Y. H. & HALLETT, M. 2004. Disturbed surround inhibition in focal hand dystonia. *Ann Neurol,* 56**,** 595-9.

SPENCE, C. 2014. The skin as a medium for sensory substitution. *Multisens Res,* 27**,** 293-312.

SPULER, M., WALTER, A., RAMOS-MURGUIALDAY, A., NAROS, G., BIRBAUMER, N., GHARABAGHI, A., ROSENSTIEL, W. & BOGDAN, M. 2014. Decoding of motor intentions from epidural ECoG recordings in severely paralyzed chronic stroke patients. *J Neural Eng,* 11**,** 066008.

TABAKOW, P., RAISMAN, G., FORTUNA, W., CZYZ, M., HUBER, J., LI, D., SZEWCZYK, P., OKUROWSKI, S., MIEDZYBRODZKI, R., CZAPIGA, B., SALOMON, B., HALON, A., LI, Y., LIPIEC, J., KULCZYK, A. & JARMUNDOWICZ, W. 2014. Functional regeneration of supraspinal connections in a patient with transected spinal cord following transplantation of bulbar olfactory ensheathing cells with peripheral nerve bridging. *Cell Transplant*.

TABOT, G. A., DAMMANN, J. F., BERG, J. A., TENORE, F. V., BOBACK, J. L., VOGELSTEIN, R. J. & BENSMAIA, S. J. 2013. Restoring the sense of touch with a prosthetic hand through a brain interface. *Proc Natl Acad Sci U S A,* 110**,** 18279-84.

TAMURA, Y., UEKI, Y., LIN, P., VORBACH, S., MIMA, T., KAKIGI, R. & HALLETT, M. 2009. Disordered plasticity in the primary somatosensory cortex in focal hand dystonia. *Brain,* 132**,** 749-55.

TARSY, D. & SIMON, D. K. 2006. Dystonia. *N Engl J Med,* 355**,** 818-29.

TEMPEL, L. W. & PERLMUTTER, J. S. 1990. Abnormal vibration-induced cerebral blood flow responses in idiopathic dystonia. *Brain,* 113 (Pt 3)**,** 691-707.

THAYER, Z. C. & JOHNSON, B. W. 2006. Cerebral processes during visuo-motor imagery of hands. *Psychophysiology,* 43**,** 401-12.

THOMPSON, R. F. & STEINMETZ, J. E. 2009. The role of the cerebellum in classical conditioning of discrete behavioral responses. *Neuroscience,* 162**,** 732-55.

THOMSON, E. E., CARRA, R. & NICOLELIS, M. A. 2013. Perceiving invisible light through a somatosensory cortical prosthesis. *Nat Commun,* 4**,** 1482.

TINAZZI, M., FARINA, S., EDWARDS, M., MORETTO, G., RESTIVO, D., FIASCHI, A. & BERARDELLI, A. 2005a. Task-specific impairment of motor cortical excitation and inhibition in patients with writer's cramp. *Neurosci Lett,* 378**,** 55-8.

TINAZZI, M., FIASCHI, A., FRASSON, E., FIORIO, M., CORTESE, F. & AGLIOTI, S. M. 2002. Deficits of temporal discrimination in dystonia are independent from the spatial distance between the loci of tactile stimulation. *Mov Disord,* 17**,** 333-8.

TINAZZI, M., FIORIO, M., BERTOLASI, L. & AGLIOTI, S. M. 2004. Timing of tactile and visuo-tactile events is impaired in patients with cervical dystonia. *J Neurol,* 251**,** 85-90.

TINAZZI, M., FIORIO, M., FIASCHI, A., ROTHWELL, J. C. & BHATIA, K. P. 2009. Sensory functions in dystonia: insights from behavioral studies. *Mov Disord,* 24**,** 1427-36.

TINAZZI, M., FRASSON, E., POLO, A., TEZZON, F., BOVI, P., DEOTTO, L., MAUGUIERE, F., FIASCHI, A. & FERRARI, G. 1999. Evidence for an abnormal cortical sensory processing in dystonia: selective enhancement of lower limb P37-N50 somatosensory evoked potential. *Mov Disord,* 14**,** 473-80.

TINAZZI, M., STANZANI, C., FIORIO, M., SMANIA, N., MORETTO, G., FIASCHI, A., EDWARDS, M. J., BHATIA, K. P. & ROTHWELL, J. C. 2005b. Temporal discrimination of two passive movements in humans: a new psychophysical approach to assessing kinaesthesia. *Exp Brain Res,* 166**,** 184-9.

TOMASINO, B., BORRONI, P., ISAJA, A. & RUMIATI, R. I. 2005. The role of the primary motor cortex in mental rotation: a TMS study. *Cogn Neuropsychol,* 22**,** 348-63.

TREMBLAY, F., LEONARD, G. & TREMBLAY, L. 2008. Corticomotor facilitation associated with observation and imagery of hand actions is impaired in Parkinson's disease. *Exp Brain Res,* 185**,** 249-57.

TUCKER, M. R., OLIVIER, J., PAGEL, A., BLEULER, H., BOURI, M., LAMBERCY, O., MILLAN JDEL, R., RIENER, R., VALLERY, H. & GASSERT, R. 2015. Control strategies for active lower extremity prosthetics and orthotics: a review. *J Neuroeng Rehabil,* 12**,** 1.

TUMAS, V. & SAKAMOTO, A. C. 2009. A kinesthetic motor imagery study in patients with writer' cramp. *Arq Neuropsiquiatr,* 67**,** 396-401.

USAKLI, A. B., GURKAN, S., ALOISE, F., VECCHIATO, G. & BABILONI, F. 2010. On the use of electrooculogram for efficient human computer interfaces. *Comput Intell Neurosci***,** 135629.

VAN BOVEN, R. W. & JOHNSON, K. O. 1994. The limit of tactile spatial resolution in humans: grating orientation discrimination at the lip, tongue, and finger. *Neurology,* 44**,** 2361-6.

VAN DEN BRAND, R., HEUTSCHI, J., BARRAUD, Q., DIGIOVANNA, J., BARTHOLDI, K., HUERLIMANN, M., FRIEDLI, L., VOLLENWEIDER, I., MORAUD, E. M., DUIS, S., DOMINICI, N., MICERA, S., MUSIENKO, P. & COURTINE, G. 2012. Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science,* 336**,** 1182-5.

VAN NUENEN, B. F., HELMICH, R. C., BUENEN, N., VAN DE WARRENBURG, B. P., BLOEM, B. R. & TONI, I. 2012. Compensatory activity in the extrastriate body area of Parkinson's disease patients. *J Neurosci,* 32**,** 9546-53.

VAUGHAN, T. M. & WOLPAW, J. R. 2006. The Third International Meeting on Brain-Computer Interface Technology: making a difference. *IEEE Trans Neural Syst Rehabil Eng,* 14**,** 126-7.

VELLISTE, M., PEREL, S., SPALDING, M. C., WHITFORD, A. S. & SCHWARTZ, A. B. 2008. Cortical control of a prosthetic arm for self-feeding. *Nature,* 453**,** 1098-101.

VENKATRAMAN, S., ELKABANY, K., LONG, J. D., YAO, Y. & CARMENA, J. M. 2009. A system for neural recording and closed-loop intracortical microstimulation in awake rodents. *IEEE Trans Biomed Eng,* 56**,** 15-22.

VIDAILHET, M., DUPEL, C., LEHERICY, S., REMY, P., DORMONT, D., SERDARU, M., JEDYNAK, P., VEBER, H., SAMSON, Y., MARSAULT, C. & AGID, Y. 1999. Dopaminergic dysfunction in midbrain dystonia: anatomoclinical study using 3-dimensional magnetic resonance imaging and fluorodopa F 18 positron emission tomography. *Arch Neurol,* 56**,** 982-9.

VIDAL, J. J. 1973. Toward direct brain-computer communication. *Annu Rev Biophys Bioeng,* 2**,** 157-80.

VIDAURRE, C. & BLANKERTZ, B. 2010. Towards a cure for BCI illiteracy. *Brain Topogr,* 23**,** 194-8.

VIDAURRE, C., SANNELLI, C., MULLER, K. R. & BLANKERTZ, B. 2011. Co-adaptive calibration to improve BCI efficiency. *J Neural Eng,* 8**,** 025009.

WANDER, J. D. & RAO, R. P. 2014. Brain-computer interfaces: a powerful tool for scientific inquiry. *Curr Opin Neurobiol,* 25**,** 70-5.

WANG, S., WANG, L., MEIJNEKE, C., VAN ASSELDONK, E., HOELLINGER, T., CHERON, G., IVANENKO, Y., LA SCALEIA, V., SYLOS-LABINI, F., MOLINARI, M., TAMBURELLA, F., PISOTTA, I., THORSTEINSSON, F., ILZKOVITZ, M., GANCENT, J., NEVATIA, Y., HAUFFE, R., ZANOW, F. & VAN DER KOOIJ, H. 2014. Design and Control of the MINDWALKER Exoskeleton. *IEEE Trans Neural Syst Rehabil Eng*.

WANG, W., COLLINGER, J. L., DEGENHART, A. D., TYLER-KABARA, E. C., SCHWARTZ, A. B., MORAN, D. W., WEBER, D. J., WODLINGER, B., VINJAMURI, R. K., ASHMORE, R. C., KELLY, J. W. & BONINGER, M. L. 2013. An electrocorticographic brain interface in an individual with tetraplegia. *PLoS One,* 8**,** e55344.

WINDISCHBERGER, C., LAMM, C., BAUER, H. & MOSER, E. 2003. Human motor cortex activity during mental rotation. *Neuroimage,* 20**,** 225-32.

WOLPAW, J. & WOLPAW, E. W. 2012. *Brain-computer interfaces: principles and practice*, Oxford University Press.

WOLPAW, J. R., BIRBAUMER, N., MCFARLAND, D. J., PFURTSCHELLER, G. & VAUGHAN, T. M. 2002. Brain-computer interfaces for communication and control. *Clin Neurophysiol,* 113**,** 767-91.

WOLPAW, J. R., LOEB, G. E., ALLISON, B. Z., DONCHIN, E., DO NASCIMENTO, O. F., HEETDERKS, W. J., NIJBOER, F., SHAIN, W. G. & TURNER, J. N. 2006. BCI Meeting 2005--workshop on signals and recording methods. *IEEE Trans Neural Syst Rehabil Eng,* 14**,** 138-41.

WOLPAW, J. R. & MCFARLAND, D. J. 2004. Control of a two-dimensional movement signal by a noninvasive brain-computer interface in humans. *Proceedings of the National Academy of Sciences of the United States of America,* 101**,** 17849-17854.

WOLPERT, D. M. 1997. Computational approaches to motor control. *Trends Cogn Sci,* 1**,** 209-16.

WOLPERT, D. M. & GHAHRAMANI, Z. 2000. Computational principles of movement neuroscience. *Nature neuroscience,* 3 Suppl**,** 1212-7.

WOLPERT, D. M., GHAHRAMANI, Z. & JORDAN, M. I. 1995. An internal model for sensorimotor integration. *Science,* 269**,** 1880-2.

WOLPERT, D. M., GOODBODY, S. J. & HUSAIN, M. 1998. Maintaining internal representations: the role of the human superior parietal lobe. *Nat Neurosci,* 1**,** 529-33.

WRAGA, M., THOMPSON, W. L., ALPERT, N. M. & KOSSLYN, S. M. 2003. Implicit transfer of motor strategies in mental rotation. *Brain Cogn,* 52**,** 135-43.

YANAGISAWA, T., HIRATA, M., SAITOH, Y., KISHIMA, H., MATSUSHITA, K., GOTO, T., FUKUMA, R., YOKOI, H., KAMITANI, Y. & YOSHIMINE, T. 2012. Electrocorticographic control of a prosthetic arm in paralyzed patients. *Ann Neurol,* 71**,** 353-61.

YIN, E., ZHOU, Z., JIANG, J., CHEN, F., LIU, Y. & HU, D. 2013. A novel hybrid BCI speller based on the incorporation of SSVEP into the P300 paradigm. *J Neural Eng,* 10**,** 026012.

ZACKS, J. M. 2008. Neuroimaging studies of mental rotation: a meta-analysis and review. *J Cogn Neurosci,* 20**,** 1-19.

ZEMELMAN, B. V., LEE, G. A., NG, M. & MIESENBOCK, G. 2002. Selective photostimulation of genetically chARGed neurons. *Neuron,* 33**,** 15-22.

ZEUNER, K. E., BARA-JIMENEZ, W., NOGUCHI, P. S., GOLDSTEIN, S. R., DAMBROSIA, J. M. & HALLETT, M. 2002. Sensory training for patients with focal hand dystonia. *Ann Neurol,* 51**,** 593-8.

ZEUNER, K. E. & HALLETT, M. 2003. Sensory training as treatment for focal hand dystonia: a 1-year follow-up. *Mov Disord,* 18**,** 1044-7.

ZIEGLER-GRAHAM, K., MACKENZIE, E. J., EPHRAIM, P. L., TRAVISON, T. G. & BROOKMEYER, R. 2008. Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil,* 89**,** 422-9.

ZOONS, E., BOOIJ, J., NEDERVEEN, A. J., DIJK, J. M. & TIJSSEN, M. A. 2011. Structural, functional and molecular imaging of the brain in primary focal dystonia--a review. *Neuroimage,* 56**,** 1011-20.

9. Attached publication:

Differential neural encoding of sensorimotor and visual body representations.

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Differential neural encoding of sensorimotor and visual body representations

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Sensorimotor processing specifically impacts mental body representations. In particular, deteriorated somatosensory input (as after complete spinal cord injury) increases the relative weight of visual aspects of body parts' representations, leading to aberrancies in how images of body parts are mentally manipulated (e.g. mental rotation). This suggests that a sensorimotor or visual reference frame, respectively, can be relatively dominant in local (hands) versus global (full-body) bodily representations. On this basis, we hypothesized that the recruitment of a specific reference frame could be reflected in the activation of sensorimotor versus visual brain networks. To this aim, we directly compared the brain activity associated with mental rotation of hands versus full-bodies. Mental rotation of hands recruited more strongly the supplementary motor area, premotor cortex, and secondary somatosensory cortex. Conversely, mental rotation of full-bodies determined stronger activity in temporo-occipital regions, including the functionally-localized extrastriate body area. These results support that (1) sensorimotor and visual frames of reference are used to represent the body, (2) two distinct brain networks encode local or global bodily representations, and (3) the extrastriate body area is a multimodal region involved in body processing both at the perceptual and representational level.

Human beings can effortlessly recall perceptions even in absence of the appropriate sensory information[1], e.g. when we mentally evoke a familiar landscape. Commonly defined as "mental imagery", such a mental reproduction of physical objects' properties is not limited to perception, but also it extends to movements[2]. In this case it is defined "motor imagery" and is characterized by the activation of sensorimotor representations even in absence of overt execution[3]. Since the dawn of experimental psychology, a particular interest in motor imagery has driven the attention of the precursors of today's cognitive neuroscience. Alexander Bain's "Simulation Theory"[4] proposed that motor imagery and overt movements rely on similar cognitive mechanisms and neural underpinnings. More recent evidence supports this view, showing that the time to imagine and perform a specific action is proportional[5], and that imagined and executed movements activate partially overlapping brain networks[6].

An objective measurement of the temporal properties of motor imagery is provided by a cognitive task called "mental rotation", in which participants judge the laterality of rotated images while response times (RTs) and accuracy are recorded[7]. In case of bodily images, mental rotation depends on the nature of the images. When hand images are mentally rotated, the performance strongly depends on image orientation (RTs linearly increase from 0° to 180° rotation and vice versa until 360°)[8] and is influenced by actual proprioceptive input[9]. Conversely, mental rotation of full-bodies is less dependent on orientation[10] and proprioception[11]. In addition, the absence of proprioceptive input (as after complete spinal cord injury) affects the interplay between visual and sensorimotor components in the representation of the disconnected body parts (feet, in the case of complete spinal cord injury)[12]. Thus, previous work suggests that mental rotation of local bodily images (hands) recruits mainly sensorimotor mechanisms, while mental rotation of global bodily images (full-bodies) is mostly based on visual mechanisms. On this basis, it can be hypothesized that, at the neural level, mental rotation of hands would be associated with the activation of prefrontal, pre-central, and post-central regions, while mental rotation of full-bodies would recruit more strongly the temporo-occipital cortex. Only very few studies compared mental rotation of body parts and full-bodies, only behavioral data were recorded, and the two classes of used images differed in terms of visual

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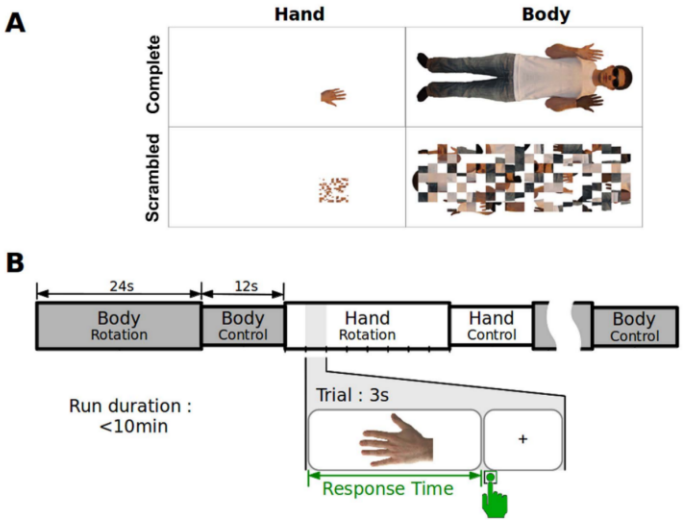

Figure 1. Stimuli and Procedure. (A) Experimental Images. Each image was presented twice, either complete or scrambled. **(B)** Schematic representation of an experimental run. During the "rotation" blocks, complete images were presented and participants performed mental rotation. During the "control" block, scrambled images were presented and merely observed by the participants. The bottom line shows an example of mental rotation trial.

aspects of the target item[13,14]. To provide relevant information about the neural substrates encoding local (hands) *versus* global (full-bodies) bodily representations, we studied the behavioral and neuroimaging counterparts of mental rotation of hands and full-bodies, in a within-subject fashion, and with comparable visual stimuli.

Different studies investigated the neural underpinnings of mental rotation of either hands or full-bodies, separately. Mental rotation of hands has been associated with activity in prefrontal, precentral, postcentral, and parietal regions[15–17]. Conversely, mental rotation of full-bodies activated mainly temporo-parieto-occipital regions[18], including the so-called extrastriate body area (EBA) located in the middle-inferior temporo-occipital gyrus[19]. This evidence suggests that distinct neural networks are specialized to process local *versus* global body representations, in that local representations are based on a sensorimotor frame of reference while global representations on a visual one. However, these assumptions must be considered with caution, as none of the previous studies performed a direct and within-subject comparison between the brain activity associated with mental rotation of hands versus full-bodies. Such a direct comparison might reveal the neural counterparts of this behaviorally-based theory. To better clarify the neuro-cognitive mechanisms associated with local and global aspects of body representation, in a within-subject fashion, we recorded brain activity while healthy participants judged the laterality of pictures of hands and full-bodies presented in different orientations from upright (which implies mental rotation). To exclude potential biases due to visual aspects of the images, we extracted the hand image from the full-body one. Thus, the target images (hands for both hand and full-body stimuli) were perfectly comparable in terms of gender, age, race, posture, etc. (Fig. 1A). This approach allowed us to provide objective measurements of both the behavioral and neural responses associated with mental processing of local *versus* global body representations, with eminent insights onto the interplay between sensorimotor and visual frames of reference involved in body representation.

Results

Behavior. In accordance with previous studies[11], RTs were analyzed by means of a 3-way repeated measures ANOVA with stimulus (hands, full-bodies), laterality (left, right), and orientation (0°, 90°, 180°, and 270°) as main factors. The 2-way interaction between stimulus and orientation was significant [$F(3,45) = 11.8$; $p < 0.05$]. For both hands and full-bodies, the RTs for stimuli presented at 180° were longer with respect to all the other orientations (all $p < 0.05$). Interestingly, the Bonferroni corrected post-hoc comparisons showed that, for images presented at 0°, participants were faster in mentally rotating hands (1037 ms) than full-bodies (1180 ms, $p < 0.05$). Conversely, for images presented at 180°, participants were significantly faster ($p < 0.05$) with full-bodies (1350 ms) than hands (1519 ms) (Fig. 2). Thus, in line with previous evidence, the mental rotation function (non-monotonical increase of RTs as a function of stimulus orientation) was more pronounced for hands than full-bodies[11]. Further behavioral effects generally confirmed previous work and are reported in detail as Supplementary Material (results).

Brain Activity. All the activated clusters and related statistics are reported in Table 1 and graphically represented in Fig. 3. To dissociate the brain activity associated with visual perception from mental representation of

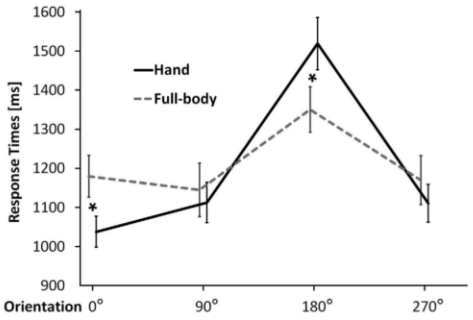

Figure 2. Stimulus-dependent modulation of the mental rotation function. Mean response times (RTs) as a function of stimulus and orientation. With respect to mental rotation of full-bodies, mental rotation of hands is more strongly affected by the orientation of the images. Error bars represent standard errors. Asterisks represent significant differences between hands and full-bodies ($p < 0.05$).

Region	Hemisphere	T-value	Cluster size (voxels)	Peak (MNI)		
				x	*y*	*z*
Hand > Body						
SMA	L	5.24	28	−4	22	60
	R	4.26	6	8	−2	62
PMC	L	7.01	99	−22	−16	66
	R	5.63	11	32	−18	66
SII	L	6.49	59	−58	−30	34
	L	4.53	11	−40	−30	40
BG	L	5.78	60	−16	10	2
	R	5.76	43	18	12	2
Body > Hand						
MOG	R	13.84	547	26	−94	12
MOG	L	13.01	210	−16	−102	8
FG	L	4.95	36	−36	−48	−16
EBA	L	4.02	7	−42	−84	−6

Table 1. Activated clusters. Regions more strongly activated during mental rotation of hands with respect to full-bodies were included in the sensorimotor network. The visual network was more active during mental rotation of full-bodies with respect to hands.

the experimental images, in two control conditions participants observed the scrambled versions of the hand and the full-body images, respectively (Fig. 1A). On this basis, the contrast hands > full-bodies showed the regions predominantly activated during mental rotation of hands with respect to mental rotation of full-bodies ($t > 4.26$; $p < 0.05$; FDR corrected). These regions were part of the sensorimotor network and comprised, bilaterally, the supplementary motor area (SMA), premotor cortex (PMC), and basal ganglia (BG), plus the left secondary somatosensory cortex (SII). In the left hemisphere, the left-SMA cluster (250 mm^3) was located in the medial frontal lobe (95% of the voxels) and comprised BA 8 (83% of the voxels). The left-PMC (923 mm^3) cluster was located in the precentral gyrus (93%) and comprised BA 6 (99%). The left-BG cluster (583 mm^3) was located in the left putamen (72%), caudate nucleus (18%), internal capsula (7%) and pallidum (1%). The left-SII cluster comprised two sub-clusters. The first SII sub-cluster (564 mm^3) was located in the supramarginal gyrus (79%) and inferior parietal lobule (21%) and comprised BA 2 (65%) and BA 48 (28%). The second SII sub-cluster (105 mm^3) was located in the inferior parietal lobule (83%) and the postcentral gyrus (16%) and comprised BA 2 and BA 3 (49% and 48%). In the right hemisphere, the right-SMA cluster (56 mm^3) was located in the medial frontal lobe (100%, BA 6). The right-PMC cluster (105 mm^3) was located in the precentral gyrus (100%, BA 6). The right-BG cluster (423 mm^3) was located in the putamen (47%), caudate (24%), internal capsula (21%), and pallidum (5%).

The opposite contrast, full-bodies > hands, showed the brain areas more strongly activated during mental rotation of full-bodies (with respect to hands), namely the visual network. These clusters were located within the regions identified by the EBA-functional localizer ($t > 4$; $p < 0.05$; FDR corrected), and included the middle occipital gyrus (MOG), fusiform gyrus (FG), and EBA in the left hemisphere, as well as the MOG in the right hemisphere. The left-MOG cluster (1977 mm^3) included the MOG (70%), the inferior occipital gyrus (11%), the calcarine cortex (8%), and the superior occipital gyrus (4%). This cluster comprised BA 18 (60%) and BA 17 (36%). The left-FG cluster (355 mm^3) covered the FG (81%) and the inferior temporal gyrus (18%). This cluster

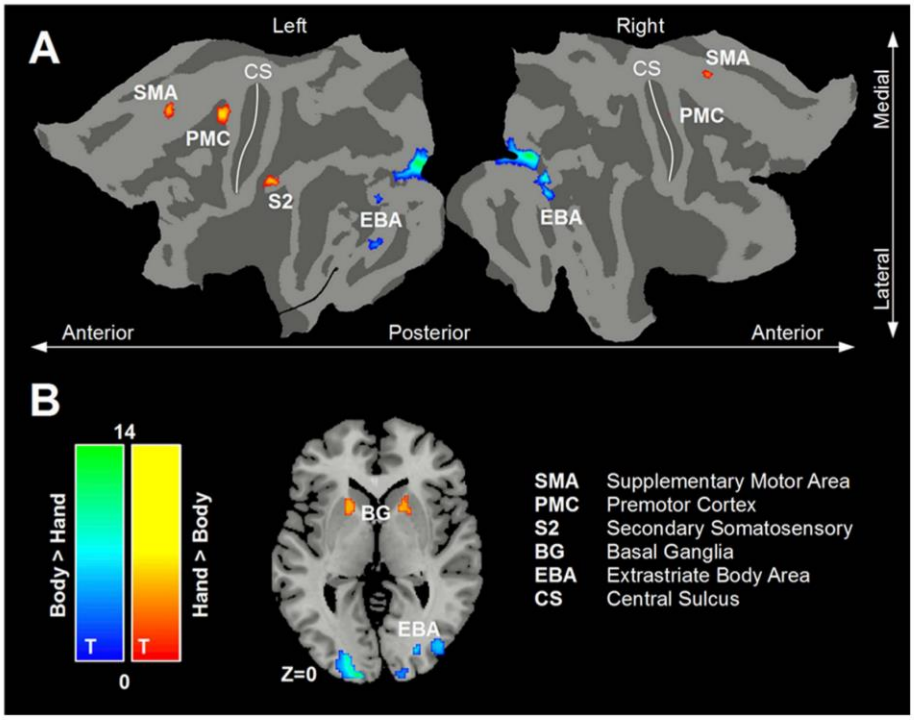

Figure 3. Local vs. global body representations. Direct comparison between the brain activity elicited by mental rotation of hands versus full-bodies. Mental rotation of hands (local body representations) activated the sensorimotor network (red-to-yellow). Mental rotation of full-bodies was associated with stronger activity within the visual network, including the extrastriate body area (blue-to-green). Activation clusters included both (**A**) cortical regions, represented on a flattened brain surface, and (**B**) subcortical regions represented on an axial brain slice.

was almost entirely located in BA 37 (99%). The left-EBA cluster (54 mm^3), covered the inferior occipital gyrus (58%) and the MOG (26%), and comprised BA19 (81%). The right-MOG cluster (5117 mm3) covered the MOG (38%), inferior occipital gyrus (20%), inferior temporal gyrus (13%), superior occipital gyrus (9%), cuneus (5%), and FG (4%). This cluster comprised BA 18 (35%), BA 19 (34%), BA 17 (15%), and BA 37 (11%). Thus, mental rotation of full-bodies bilaterally activated parts of the inferior occipital gyrus corresponding to the functionally defined EBA (Fig. 4).

Discussion

Human beings automatically create local and global mental representations of the body, e.g. to adequately interact with the environment. The integrity of such bodily representations is not obvious and requires the proper functioning of specific neural mechanisms. Here, we report neuro-behavioral data showing that two distinct patterns of cortical activity are selectively associated with mental representation of local body-parts *versus* global whole-body. We assessed the characteristics of local and global body representations by implicitly asking participants to mentally rotate images of hands and full-bodies, respectively. The behavioral data showed that the profile of mental rotation of hands (distribution of RTs as a function of image orientation) was more strongly influenced by anatomically relevant constraints, with respect to full-bodies. At the neural level, the direct and two-way comparison between mental rotation of hands and full-bodies indicated the stronger activation of a set of sensorimotor regions during mental rotation of hands (with respect to full-bodies), and the stronger activation of a set of visual regions during mental rotation of full-bodies (with respect to hands). Only two studies investigated the differences between mental rotation of body parts and full-bodies in healthy[13] or clinical populations[14]. These studies recorded only behavioral data and used different classes of images for the two categories. Thus, to our knowledge the present study is the first to directly compare, in a within-subject fashion, and with comparable target stimuli, the behavioral and neuroimaging data related to local (hands) *versus* global (full-bodies) body representations. The present data support that local body representations are more strongly based on sensorimotor processing, possibly extending to movement simulation mechanisms[20]. Conversely, global body representations are more robustly based on visual processing, possibly involving mainly components of visuo-spatial reasoning[18]. Unraveling the neuro-behavioral basis of the distinction between local (sensorimotor) and global (visual) bodily representations, we provide a detailed view of where different aspects of body representation are distinctly processed in the human brain. The present findings can

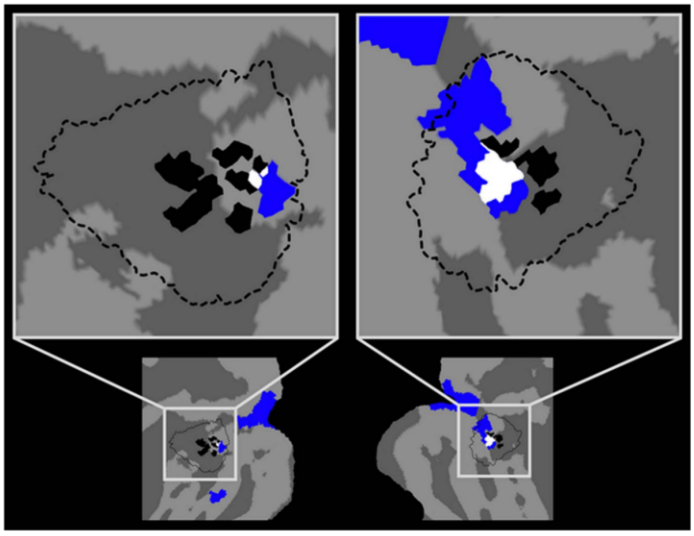

Figure 4. EBA localization. Overlap (white) between the brain activity during mental rotation of full-bodies within the functionally localized EBA (blue) and the peak activity voxels reported in 30 previous studies (black) (Supplementary Table S1). Both the overlap and the activation due to mental rotation of full-bodies were comprised within the regions (dashed line) typically described as EBA (Supplementary Table S1).

have important clinical benefits, offering the baseline reference framework and the experimental approach to assess, monitor, and restore possibly distorted body representations as a consequence of e.g. neural injury and/or degeneration[21,22].

Mental rotation of hands and the sensorimotor network. The present behavioral data show that mental rotation of hands was strongly affected by image orientation, leading to a non-monotonic increase of the RTs profile at 180°[23]. Such a dependency on orientation is considered a sign of the recruitment of sensorimotor mechanisms[24], i.e. the simulation of the movement through which one could place one's own body part in the position of the image[25]. On this basis, our behavioral data confirm the key role of sensorimotor mechanisms in hand-centered mental representations[26]. This interpretation is further supported by our neuroimaging data. Indeed, we found that the sensorimotor network increased its activity during mental rotation of hands, including SMA, PMC, SII, and BG. These regions have been consistently associated with mental rotation of hands. While the most common view links mental rotation of hands to activity in SMA and PMC[16,27,28], different studies highlighted the importance of other regions of the sensorimotor network, including SII[15], and BG[29]. Linking regions previously reported in isolation, our results further extend this evidence by showing that these regions work in parallel, as parts of a widespread network. These findings indicate that local body representations are encoded by the activity of not only specific regions, as previously shown, but also by a widespread brain network including both cortical and subcortical structures and selectively centered on the sensorimotor system.

Why should such a large network be necessary for a relatively simple task such as mental rotation of body parts? It is worth noting that many different aspects of body representation are simultaneously processed during mental rotation. Based on the Simulation Theory, during mental rotation of body parts we use our own body as a reference and we simulate the movement that would bring our body part into the position of the displayed body part. To this aim, we have to know where our body part is located with respect to the body and, hence, have to plan the necessary movement. Thus, at least two aspects are involved in this sensorimotor simulation: one (somatosensory) aspect is more focused on retrieving information on the actual state of the body part; another (motor) aspect is more focused on the transition from the actual status (our own body part) to the target status (as the displayed body part). In this vein, we interpret the activation of the sensorimotor network as the result of both somatosensory and motor components of mental rotation of hands. In particular, for the somatosensory component, we found activity in SII. This region plays an important role in encoding the position of a body part with respect to the whole body both in humans[15] and non-human primates[30] and it has been involved in movement execution, observation, and simulation[31]. Accordingly, we interpret the activation of SII as the neural counterpart of encoding the actual (somatosensory) state of the hand with respect to the body, to be further used as reference by the motor component. Indeed, during mental simulation of movements, SII increases its functional connectivity with SMA[32] and we found activation of SMA and PMC. This latter possibly encodes the motor aspect of mental rotation. This is in line with previous studies which used similar experimental protocols and observed the activation of SMA[28] and PMC[33]. During mental rotation of hands we also found the activation of BG. It is worth noting that BG project to prefrontal regions[34], are consistently reported by studies on motor imagery[35], and their lesion is associated with impaired performance in motor imagery tasks[36]. On this basis, we interpret the activation

of SMA, PMC, and BG as the neural counterpart of the motor component of mental rotation. Considering that mental rotation of hands is just one of the tasks used to activate local body representations, we propose that local body representations comprise at least these two components (somatosensory and motor) and that there is a continuous and mutual exchange of information between them[37]. Due to the intrinsic limitations of fMRI and the experimental protocol, we could not disentangle temporal features of the recorded brain activity (which regions are activated first). Further studies are required to clarify this important point, using an investigation technique, such as EEG, specifically designed to understand temporal dynamics of cognitive processes.

Mental rotation of full-bodies and the visual network. Consistently with previous studies[13], here we found that mental rotation of full-bodies was weakly affected by the orientation of the image. Considering the stronger impact of orientation on mental rotation of hands (despite the fact that the target hand was exactly the same in both stimuli), these data could be the result of the adoption of two different strategies: "effector-based" versus "perspective" mental transformations, respectively. While effector-based transformations use an egocentric frame of information processing, perspective transformations use an allocentric frame of reference and show higher degrees of physical flexibility[26], are less influenced by biomechanical constraints[38], and are less affected by anatomical plausibility[39]. Along this line, if a stereotyped "head" is drawn on the abstract objects typically used in mental rotation studies[41], the impact of stimulus orientation decreases[40]. Thus, mental rotation of hands should trigger an effector-based transformation, which could result in the activation of mostly somatosensory and kinesthetic representations. Conversely, the full-bodies should elicit perspective transformations and predominantly activate visuo-spatial representations[42]. In support of this view, the present EBA activation shows that mental rotation of full-bodies selectively activates visuo-spatial representations of the body encoded by higher regions of the visual brain network.

Typically, EBA is functionally defined, thus its exact location varies across different studies and different designs[43]. The location of the present EBA-clusters reasonably overlapped with the stereotaxic location of EBA in previous studies[44]. In particular, the coordinates of the present EBA clusters' centroid were within the range defined by 30 previous studies (Table S1). On this basis, we propose that we identified EBA and that this region is part of the neural substrate implied in processing mental whole-body representations. Interestingly, in a region anatomically overlapping with our EBA, the pattern of activity is parametrically modulated as a function of the speed of mental rotation of bodies[45]. However, any conclusion about EBA based on the results of this last study[45] has to be considered with caution, due to the absence of an EBA-specific functional localizer. Using a EBA-specific functional localizer, we found that mental rotation of bodies (but not hands) recruited EBA. Previous studies showed that EBA, on the one hand, contributes to the creation of the sense of owning and being situated within a body[46,47]. On the other hand, it is involved in allocentric body representations[48], regardless of the identity of the visualized body (oneself or another person)[49]. Thus, EBA could be responsible for the generation of body ownership in allocentric perspectives, independent from body identity. On this basis, we propose that the stronger activation of EBA during mental rotation of bodies could be a sign that participants embodied the full-body image presented in allocentric perspective. This view extends the functions of EBA to the representational level for body ownership during allocentric perspective taking.

What is the exact role of EBA at the representational level? A previous study fostered the idea that EBA is involved in creating detail-based body representations (body parts)[50]. Conversely, our data show that EBA is activated by whole-body stimuli, and not body parts. This apparent inconsistency might be due to differences in experimental designs, scanning procedures, or data analyses. For instance, while in the study by Costantini *et al.*[50], the stimuli comprised only body parts, here we directly compared mental rotation of body parts (hand) and full-bodies. In addition, Costantini *et al.*[50] used explicit imagery (participants were asked to consciously create visual images of specific body parts), while here we used implicit imagery (the laterality judgment implies mental rotation). For these reasons, on the one hand, our data support the conclusion of Costantini *et al.*[50] that EBA is involved at the representational level of body processing. On the other hand, as our task was focused on the hands also for the full-body stimuli, we further suggest that EBA plays a key role in merging piecemeal local body representations (hands) into a more complete global body representation (full-body), to be further processed by later occipito-temporal regions[51]. In this vein, the present study extends the possible functions of EBA, suggesting that it is a crucial neural hub to encode multimodal body-specific information in the process of creating (from local to global) whole-body representation.

Conclusions

The results of this study illustrate how our brain is specialized in representing visual and sensorimotor aspects of our body. Merging brain imaging and experimental psychology, we showed selective changes in the cortical patterns of activity associated with local and global body representations. These two fundamental aspects of body representation were neurally encoded by the activity of two distinct networks, i.e. sensorimotor regions for local components (hands) and the visual regions for global components (body). Importantly, the target feature of both the hand- and body-images used here, was exactly the same (the same hand was presented in isolation or attached the appropriate body). Thus, it can be concluded that the activation of the sensorimotor or visual networks was due to contextual contingencies (presence or absence of the body around the hand). The activation of the sensorimotor network during mental rotation of hands suggests the involvement of movement simulation mechanisms. The involvement of the visual network during mental rotation of bodies suggests that visuo-spatial reasoning plays a central role in this task. Accordingly, we showed that EBA, a region classically (but not exclusively) associated with visual perception of human bodies was actively involved also in the mental representation of the body. Previous studies showed that EBA is involved in a broad set of body-related functions, including visual[52] and tactile[53] perception of human bodies, execution[54] and imagination of body movements[55], and integration of multisensory bodily information[47]. The present results are in line this evidence and extend the role of EBA to the

representational level, de facto including the construction of a full-body representation in the body-related functions already attributed to EBA (e.g. motor control, multisensory integration, and body ownership). Altogether, this study provides insights for future investigation of the plastic interplay between sensorimotor and visual representations of the body as a function of individual and contextual factors, in healthy and clinical populations.

Methods

Participants. Sixteen right-handed healthy participants (7 female, 24.7 ± 3.8 y.o.) took part in the experiment. All participants had normal vision and signed a written informed consent prior to the experiment. The protocol was approved by the local Ethics Committee of the University of Zurich and the experiment was conducted in accordance with the Declaration of Helsinki 1964.

Procedure and Stimuli. The fMRI session consisted of three runs, two of which comprised blocks of mental rotation. The third run was used as a functional localizer to identify EBA in each participant. In the mental rotation runs, participants observed images of hands or full-bodies. Images were displayed in the center of the computer screen (12° × 12° of visual angle) and a projector. The projector displayed the images onto a translucent screen positioned in the MRI scanner, behind the participants' head. We used a custom-made back-projection mirror box positioned in front of the participant's eyes, inside the magnet, to visualize the images projected on the translucent screen. For the hand images, participants were instructed to judge as quickly and accurately as possible the laterality of the hand. The full-body images represented an avatar person with one darkened hand. In this case, participants judged which hand was darkened[11]. For both types of images the target hand was exactly the same (size, orientation, view, gender, age, race, etc). RT was recorded for each image and was defined as the delay between the image onset on the screen and the participant's response. Each image was presented in four different orientations (0°, 90°, 180° or 270°). All orientations were considered as clockwise rotations from the canonical upright (fingers pointing upright). The scrambled images were created by splitting the original image (hand or body) in a fixed number of squares and randomizing the position of these squares. The number of squares was the same for the hand and the body images. During the mental rotation task, the images remained visible on the screen until a response was given, with a maximum duration corresponding to one fMRI volume (3 sec). After the participant's response, the image was replaced by a fixation cross until the following trial started (Fig. 1B). Before the fMRI session, participants familiarized with the task outside the scanner. In order to avoid priming effects, the images presented during the training phase were rotated in different angles (45°, 135°, 225°, 315°) with respect to the experimental ones.

To provide responses, participants held two MRI-compatible pear-shaped pneumatic buttons, one in each hand, and clenched the left or right hand to indicate a left- or right-lateralized image. To control the motor component of this response, in a third control condition participants executed a simple stimulus-response task according to a pre-defined color coding (left or right hand clench in response to red or green square, respectively). This control condition helped us to control for any additional activation due to the hands' movement. Prior to the experiment all participants were enrolled in a training phase, including both the mental rotation and stimulus-response trials. Only after the successful completion of the training, participants were admitted to the fMRI phase. In this way we made sure that all participants were able to perform all the parts of the experiment and were not color-blind.

Each experimental run was composed of 16 blocks, each containing only one image type (hand or body). Each block comprised eight trials with all the possible combinations (left/right, and four orientations), lasting 24 s, and was followed by the presentation of the corresponding scrambled image for 12 s. The EBA functional localizer consisted in blocks of observation of bodily images interleaved with blocks of observation of an abstract shape. It was composed of 3 blocks, each containing 7 images interleaved with a blank screen, and lasting 21 seconds. After the recording of the functional brain images, a structural brain image was collected for each participant.

fMRI Data Acquisition. Functional and structural MRI scans were collected using a 3 T SIEMENS MAGNETOM Skyra scanner, operating at the University Hospital of Zurich (USZ). Each functional scan run of mental rotation comprised 200 scans, the EBA functional localizer comprised 85 scans. The following acquisition parameters were used for all functional scans: voxel size 3.0 × 3.0 × 3.5 mm, 28 interleaved slices (whole-brain coverage), TR 3 s, TE 30 ms, matrix size of 72 × 72 voxels. The T1-weighted anatomical images (0.9 mm isotropic voxels, 192 sagittal slices, TR 1.9 s, TE 4.9 ms) were collected using a magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE).

fMRI Data Analysis. fMRI data were analyzed with SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, UCL, London, UK). In accordance with standard procedures, the data preprocessing included motion correction (all participants <1.5 mm), slice-timing, coregistration, normalization, and smoothing (Supplementary Material). The time series of functional images obtained for each participant were analyzed separately. The effects of the experimental paradigm were estimated on a voxel-by-voxel basis using a general linear model[56]. Each experimental block was modeled using a boxcar, convolved with a canonical hemodynamic response function chosen to represent the relationship between neuronal activation and blood flow changes. Single-subject models were used to compute two contrast images for each participant, representing the estimated amplitude of the hemodynamic response for the hand and full-body conditions relative to the respective control conditions (scrambled images). The scrambled images of both hands and full-bodies were respectively modeled as two regressors defined as boxcar functions convolved with the hemodynamic response and therefore constituted the baseline contrasts for each corresponding experimental image. The resulting contrast images were subsequently analyzed using a random effect approach.

Cognitive tasks similar to the one used in the present study, activated the sensorimotor circuit, including the prefrontal[27], premotor[57], and secondary somatosensory cortex[15], as well as the BG[35]. On this basis, we ran a second-level region-of-interests (ROI) analysis including both functional (the EBA functional localizer) and anatomical regions (somatosensory, motor, premotor, and prefrontal cortices, plus the BG). For the functional ROI (the EBA localizer), the fMRI data were analyzed according to the task factor (observation of body *versus* abstract shape. The resulting group-level activation map was statistically corrected for False Discovery Rate (FDR) ($p < 0.01$; $t = 6.11$)[58] with a minimum cluster size of 10 voxels ($k > 10$)[59]. The anatomical ROI was created using the WFU atlas toolbox[60] implemented in SPM, and included the motor and somatosensory regions [Brodmann Areas (BA) 1, 2, 3, 4 and 6] as well as the BG. Both the functional and the anatomical ROIs were combined in a single ROI, on which the second-level analysis was performed. At the second level the two contrast images for each participant (hands > scrambled hands; full-bodies > scrambled full-bodies) were entered into a paired t-test contrast analysis with 16 pairs. Thus, for each of these two contrast images, we excluded the influence of visual processing on the resulting brain maps related to mental rotation by subtracting the brain activity associated with scrambled images. Next, we computed two direct contrasts of interest (hands > full-bodies; full-bodies > hands) to individuate the brain regions recruited more strongly during mental rotation of hands with respect to full-bodies, and vice versa. The resulting activations reflected pure mental processing, expected to be weaker than what is triggered by visual stimulation. Thus, with respect to the (visual) functional localizer, for these two main contrasts we used the same FDR correction for multiple comparisons ($p < 0.05$; $t = 4.0$) but a lower cluster size threshold ($k > 5$)[58]. In order to test the stability of the obtained results, in a stability check analysis we repeated the original second-level analysis and included the RTs as covariate in the statistical model. The activation clusters resulting from this stability check analysis were comparable to the ones resulting from the first analysis, both in terms of location and strength (Fig. S1). On this basis, we can exclude that the obtained results are significantly modulated by RTs and are rather stimulus-dependent activations.

To localize and visualize the activated clusters we used the BrainShow software[61] implemented in Matlab (The MathWorks Inc., Natick, MA, USA). In particular, we projected the group activations onto the cortical surface of the PALS atlas[62] and superimposed them to a standard template brain. Then, for each cluster, we computed the size (mm^3) and the percentage of voxels belonging to BAs and anatomical structures[63].

References

1. Di Nuovo, S., De La Cruz, V. M., Conti, D., Buono, S. & Di Nuovo, A. Mental imagery: Rehabilitation through simulation. *Life Span and Disability*. **17,** 89–118 (2014).
2. Kosslyn, S. M., Ganis, G. & Thompson, W. L. Neural foundations of imagery. *Nature Reviews Neurosci* **2,** 635–642 (2001).
3. Munzert, J., Lorey, B. & Zentgraf, K. Cognitive motor processes: the role of motor imagery in the study of motor representations. *Brain Research Reviewes* **60,** 306–326 (2009).
4. Bain, A. *The senses and the intellect*. Longman, Green, Longman, Roberts, and Green (1864).
5. Gentili, R., Han, C. E., Schweighofer, N. & Papaxanthis, C. Motor learning without doing: trial-by-trial improvement in motor performance during mental training. *Journal of Neurophysiology* **104,** 774–783 (2010).
6. Wraga, M., Thompson, W. L., Alpert, N. M. & Kosslyn, S. M. Implicit transfer of motor strategies in mental rotation. *Brain and Cognition* **52,** 135–143 (2003).
7. Cooper, L. A. & Shepard, R. N. Mental transformations in the identification of left and right hands. *Journal of Experimental Psychology: Human Perception and Performance* **104,** 48–56 (1975).
8. Parsons, L. M. Imagined spatial transformations of one's hands and feet. *Cognitive Psychology* **19,** 178–241 (1987).
9. Ionta, S., Fourkas, A. D., Fiorio, M. & Aglioti, S. M. The influence of hands posture on mental rotation of hands and feet. *Experimental Brain Research* **183,** 1–7 (2007).
10. Zacks, J. M., Mires, J., Tversky, B. & Hazeltine, E. Mental spatial transformations of objects and perspective. *Spatial Cognition and Computation* **2,** 315–332 (2002).
11. Ionta, S., Perruchoud, D., Draganski, B. & Blanke, O. Body context and posture affect mental imagery of hands. *PLoS One* **7,** e34382 (2012).
12. Ionta, S. *et al.* Spinal cord injury affects the interplay between visual and sensorimotor representations of the body. *Scientific Reports* **6,** 20144 (2016).
13. Devlin, A. L. & Wilson, P. H. Adult age differences in the ability to mentally transform object and body stimuli. Adult age differences in the ability to mentally transform object and body stimuli. *Aging, Neuropsychology, and Cognition* **17,** 709–729 (2010).
14. Tomasino, B., Toraldo, A. & Rumiati, R. I. Dissociation between the mental rotation of visual images and motor images in unilateral brain-damaged patients. *Brain and Cognition* **51,** 368–371 (2003).
15. Corradi-Dell'Acqua, C., Tomasino, B. & Fink, G. R. What is the position of an arm relative to the body? Neural correlates of body schema and body structural description. *Journal of Neuroscience* **29,** 4162–4171 (2009).
16. de Lange, F. P., Helmich, R. C. & Toni, I. Posture influences motor imagery: an fMRI study. *Neuroimage* **33,** 609–617 (2006).
17. Osuagwu, B. A. & Vuckovic, A. Similarities between explicit and implicit motor imagery in mental rotation of hands: an EEG study. *Neuropsychologia* **65,** 197–210 (2014).
18. Zacks, J. M. Neuroimaging studies of mental rotation: a meta-analysis and review. *Journal of Cognitive Neuroscience* **20,** 1–19 (2008).
19. Blanke, O., Ionta, S., Fornari, E., Mohr, C. & Maeder, P. Mental imagery for full and upper human bodies: common right hemisphere activations and distinct extrastriate activations. *Brain Topography* **23,** 321–332 (2010).
20. Miller, K. J., Schalk, G., Fetz, E. E., den Nijs, M., Ojemann, J. G. & Rao, R. P. Cortical activity during motor execution, motor imagery, and imagery-based online feedback. *Proceedings of the National Academy of Sciences*. **107(9),** 4430–4435 (2010).
21. Perruchoud, D., Pisotta, I., Carda, S., Murray, M. M. & Ionta, S. Biomimetic rehabilitation engineering: the importance of somatosensory feedback for brain–machine interfaces. *Journal of Neural Engineering*. **13(4),** 041001 (2016).
22. Pisotta, I., Perruchoud, D. & Ionta, S. Hand-in-hand advances in biomedical engineering and sensorimotor restoration. *Journal of Neuroscience Methods* **246,** 22–29 (2015).
23. Coslett, H. B., Medina, J., Kliot, D. & Burkey, A. R. Mental motor imagery indexes pain: the hand laterality task. *European Journal of Pain* **14,** 1007–1013 (2010).
24. Petit, L. S., Pegna, A. J., Mayer, E. & Hauert, C. A. Representation of anatomical constraints in motor imagery: mental rotation of a body segment. *Brain and Cognition* **51,** 95–101 (2003).
25. Jeannerod, M. Mental imagery in the motor context. *Neuropsychologia* **33,** 1419–1432 (1995).
26. Creem-Regehr, S. H., Neil, J. A. & Yeh, H. J. Neural correlates of two imagined egocentric transformations. *Neuroimage* **35** (2007).
27. Ferri, F., Frassinetti, F., Ardizzi, M., Costantini, M. & Gallese, V. A sensorimotor network for the bodily self. *Journal of Cognitive Neuroscience* **24,** 1584–1595 (2012).

28. Zapparoli, L. *et al.* Like the back of the (right) hand? A new fMRI look on the hand laterality task. *Experimental Brain Research* **232,** 3873–3895 (2014).
29. Dominey, P., Decety, J., Broussolle, E., Chazot, G. & Jeannerod, M. Motor imagery of a lateralized sequential task is asymmetrically slowed in hemi-Parkinson's patients. *Neuropsychologia* **33,** 727–741 (1995).
30. Salimi, I., Brochier, T. & Smith, A. M. Neuronal activity in somatosensory cortex of monkeys using a precision grip. I. Receptive fields and discharge patterns. *Journal of Neurophysiology* **81,** 825–834 (1999).
31. Beudel, M., Zijlstra, S., Mulder, T., Zijdewind, I. & de Jong, B. M. Secondary sensory area SII is crucially involved in the preparation of familiar movements compared to movements never made before. *Hum Brain Mapp* **32,** 564–579 (2011).
32. Chen, H., Yang, Q., Liao, W., Gong, Q. & Shen, S. Evaluation of the effective connectivity of supplementary motor areas during motor imagery using Granger causality mapping. *Neuroimage* **47,** 1844–1853 (2009).
33. Sasaoka, T., Mizuhara, H. & Inui, T. Dynamic parieto-premotor network for mental image transformation revealed by simultaneous EEG and fMRI measurement. *Journal of Cognitive Neuroscience* **26,** 232–246 (2014).
34. Middleton, F. A. & Strick, P. L. Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. *Brain and Cognition* **42,** 183–200 (2000).
35. Taube, W., Mouthon, M., Leukel, C., Hoogewoud, H. M., Annoni, J. M. & Keller, M. Brain activity during observation and motor imagery of different balance tasks: an fMRI study. *Cortex* **64,** 102–114 (2015).
36. Peterson, D. S., Pickett, K. A., Duncan, R. P., Perlmutter, J. S. & Earhart, G. M. Brain activity during complex imagined gait tasks in Parkinson disease. *Clinical Neurophysiology* **125,** 995–1005 (2014).
37. Perruchoud, D., Murray, M. M., Lefebvre, J. & Ionta, S. Focal dystonia and the Sensory-Motor Integrative Loop for Enacting (SMILE). *Frontiers in Human Neuroscience* **8,** 458 (2014).
38. Steenbergen, B., van Nimwegen, M. & Craje, C. Solving a mental rotation task in congenital hemiparesis: motor imagery versus visual imagery. *Neuropsychologia* **45,** 3324–3328 (2007).
39. Creem, S. H., Wraga, M. & Proffitt, D. R. Imagining physically impossible self-rotations: geometry is more important than gravity. *Cognition* **81,** 41–64 (2001).
40. Amorim, M. A., Isableu, B. & Jarraya, M. Embodied spatial transformations: "body analogy" for the mental rotation of objects. *Journal of Experimental Psychology: General* **135,** 327–347 (2006).
41. Shepard, R. N. & Metzler, J. Mental rotation of three-dimensional objects. *Science* **171,** 701–703 (1971).
42. Zacks, J. M. & Michelon, P. Transformations of visuospatial images. *Behavioral and Cognitive Neuroscience Reviews* **4,** 96–118 (2005).
43. de Gelder, B. *et al.* Standing up for the body. Recent progress in uncovering the networks involved in the perception of bodies and bodily expressions. *Neuroscience & Biobehavioral Reviews* **34,** 513–527 (2010).
44. Moro, V., Urgesi, C., Pernigo, S., Lanteri, P., Pazzaglia, M. & Aglioti, S. M. The neural basis of body form and body action agnosia. *Neuron* **60,** 235–246 (2008).
45. Zacks, J. M., Ollinger, J. M., Sheridan, M. A. & Tversky, B. A parametric study of mental spatial transformations of bodies. *Neuroimage* **16,** 857–872 (2002).
46. Arzy, S., Thut, G., Mohr, C., Michel, C. M. & Blanke, O. Neural basis of embodiment: distinct contributions of temporoparietal junction and extrastriate body area. *Journal of Neuroscience* **26,** 8074–8081 (2006).
47. Ionta, S. *et al.* Multisensory mechanisms in temporo-parietal cortex support self-location and first-person perspective. *Neuron* **70,** 363–374 (2011).
48. Hodzic, A., Muckli, L., Singer, W. & Stirn, A. Cortical responses to self and others. *Human Brain Mapping* **30,** 951–962 (2009).
49. Cazzato, V., Mian, E., Serino, A., Mele, S. & Urgesi, C. Distinct contributions of extrastriate body area and temporoparietal junction in perceiving one's own and others' body. *Cognitive Affective Behavioral Neuroscience* **15,** 211–228 (2015).
50. Costantini, M., Urgesi, C., Galati, G., Romani, G. L. & Aglioti, S. M. Haptic perception and body representation in lateral and medial occipito-temporal cortices. *Neuropsychologia*, **49(5),** 821–829 (2011).
51. Hodzic, A., Kaas, A., Muckli, L., Stirn, A. & Singer, W. Distinct cortical networks for the detection and identification of human body. *Neuroimage* **45,** 1264–1271 (2009).
52. Downing, P. E., Jiang, Y., Shuman, M. & Kanwisher, N. A cortical area selective for visual processing of the human body. *Science* **293,** 2470–2473 (2001).
53. Kitada, R., Johnsrude, I. S., Kochiyama, T. & Lederman, S. J. Functional specialization and convergence in the occipito-temporal cortex supporting haptic and visual identification of human faces and body parts: an fMRI study. *Journal of Cognitive Neuroscience* **21,** 2027–2045 (2009).
54. Astafiev, S. V., Stanley, C. M., Shulman, G. L. & Corbetta, M. Extrastriate body area in human occipital cortex responds to the performance of motor actions. *Nat Neurosci* **7,** 542–548 (2004).
55. Tomasino, B., Weiss, P. H. & Fink, G. R. Imagined tool-use in near and far space modulates the extra-striate body area. *Neuropsychologia* **50,** 2467–2476 (2012).
56. Worsley, K. J. & Friston, K. J. Analysis of fMRI time-series revisited–again. *Neuroimage* **2,** 173–181 (1995).
57. Helmich, R. C., de Lange, F. P., Bloem, B. R. & Toni, I. Cerebral compensation during motor imagery in Parkinson's disease. *Neuropsychologia* **45,** 2201–2215 (2007).
58. Sestieri, C. *et al.* "What" versus "where" in the audiovisual domain: an fMRI study. *Neuroimage* **33,** 672–680 (2006).
59. Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A. & Noll, D. C. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magnetic Resonamce in Medicine* **33,** 636–647 (1995).
60. Maldjian, J. A., Laurienti, P. J., Kraft, R. A. & Burdette, J. H. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* **19,** 1233–1239 (2003).
61. Galati, G. *et al.* A selective representation of the meaning of actions in the auditory mirror system. *Neuroimage*, **40,** 1274–1286 (2008).
62. Van Essen, D. C. A Population-Average, Landmark- and Surface-based (PALS) atlas of human cerebral cortex. *Neuroimage* **28,** 635–662 (2005).
63. Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B. & Joliot, M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*, **15(1),** 273–289 (2002).

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Author Contributions

The study was conceived by S.I., R.G. and L.M. The data were collected by S.I., L.M. and M.P. The statistical analyses were conducted by D.P., L.M. and S.I. The figures were created by D.P. The paper was written by D.P. and S.I. with input from L.M, M.P. and R.G. All authors reviewed the manuscript.

Additional Information

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