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CICLO XXXIII

# Revealing the invisible: quantitative analyses for studying phantom arm sensations and movements.


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*“Rem tibi quam scieris aptam dimittere noli:*

*fronte capillata, post haec occasio calva”*

*Disticha Catonis II, 26*

To my father…

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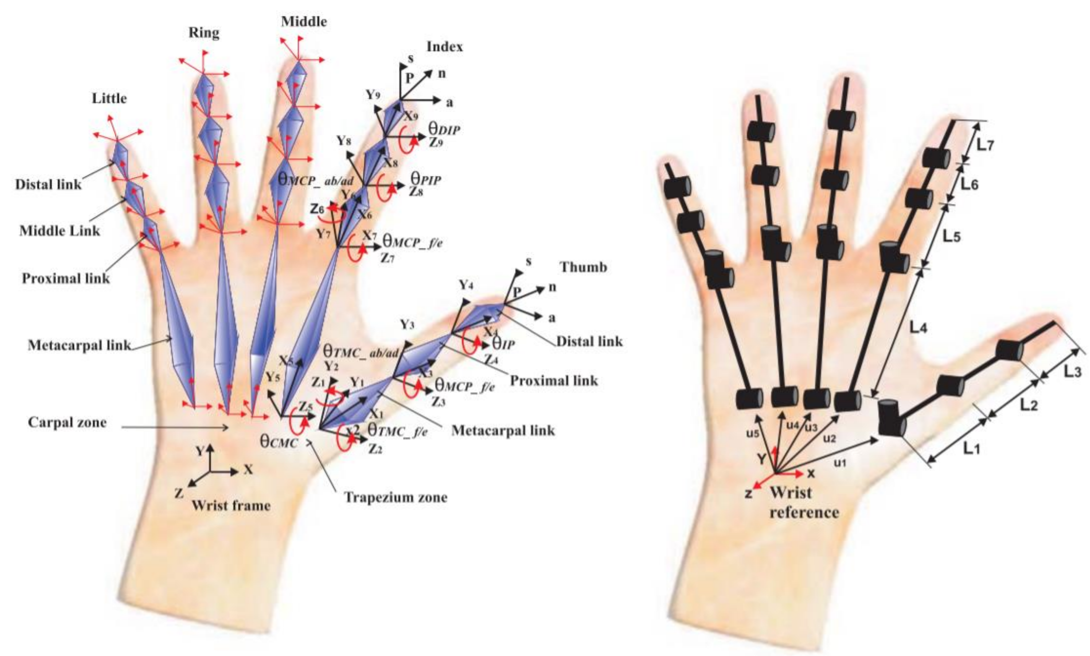
*"Many patients awaken from the anaesthetic after an amputation believing that the operation has not been performed. Their perception of the lost limb is so real. that not until they lift the bed sheets to see it do they realize it has been cut off."*

*Joel Katz, 1993*

# 1. Chapter 1: Introduction

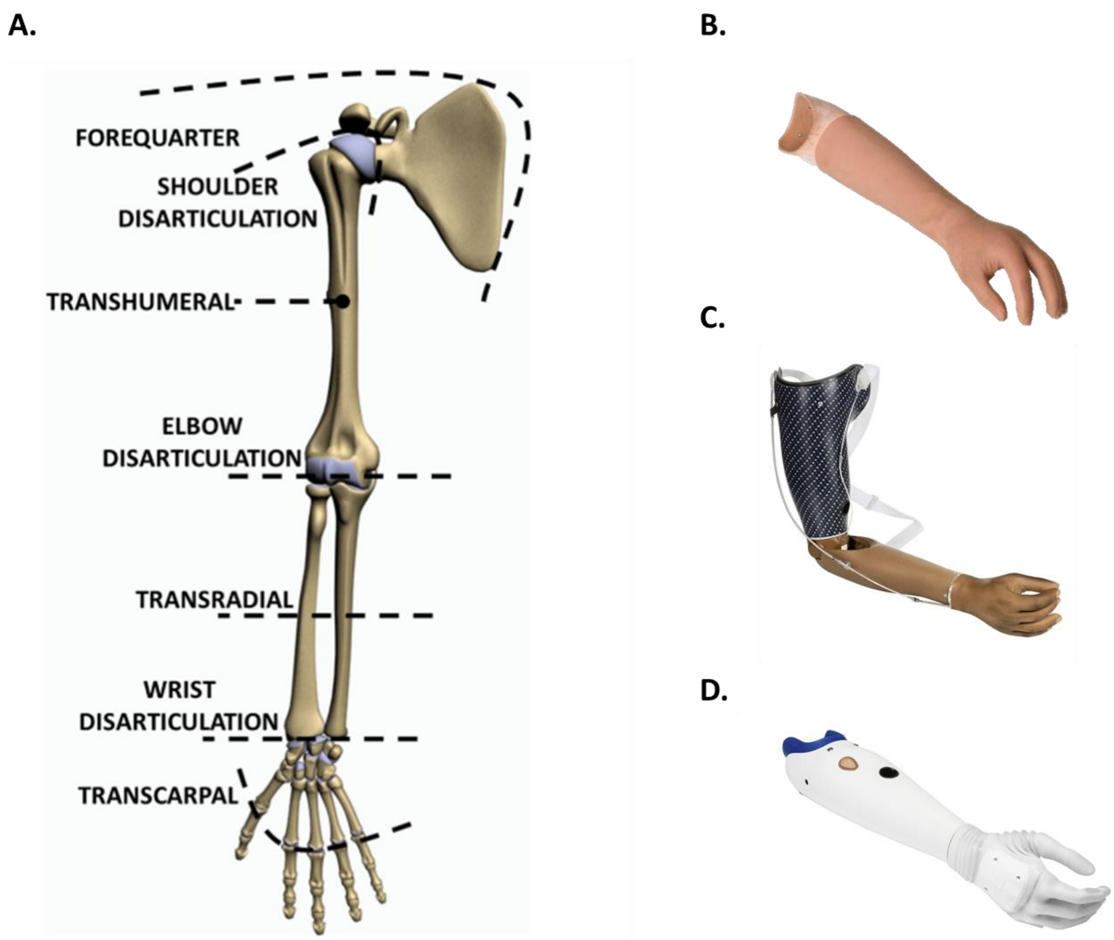
Our body is one of the most perfect machines ever created. Each single part is specifically organized and fine controlled by our operation center, the brain. The sensory-motor areas in the brain dedicates a lot of "space" to the hands as showed by the sensory-motor homunculus (Schott, 1993). Our hands are one of the most versatile parts of our body. We use them for many purposes, e.g. to talk and to act in the real world. When we speak, our hands are an important part of who we are and what we say. They can be delicate and accurate enough to paint a picture, thread a needle, or play a harp. But they can also be strong and powerful enough to swing an axe, pull a rope, or lift a table. Our hands are two important tools we have and we use them in almost every aspect of our daily lives. They allow the human beings to accomplish sophisticated movements, from power to precision tasks, thanks to the large number of Degrees of Freedom (DoFs; Figure 1.1) and the paramount role played by thumb opposition (Cordella et al., 2016).




*1.1* ***Kinematic configuration of the human hand.*** *Thumb is defined by 3 links and 4 degrees of freedom whereas index, middle, ring and little are defined by 4 links and 5 DoFs. Adapted from Cobos et al. (2008).*

For these reasons, hand amputation can be perceived as a devastating damage that can greatly worsen the life quality of the amputee. The majority of upper extremity amputation are caused by trauma, dysvascularity, orneoplasia (Raichle et al., 2008), and can be classified into partial hand amputation, wrist disarticulation, transradial (below elbow), elbow disarticulation, transhumeral (above elbow), shoulder disarticulation, and forequarter amputations (Figure 1.2A).

In the last decades, many researches and private companies have developed hand/arm prostheses that aim to, at least partially, replace the functionality of the missing hand. Hand/arm prostheses can be divided into cosmetic and active, and are used by about 80% of upper limb amputees (Østlie et al., 2012). Cosmetic prostheses (Figure 1.2B) are mainly used for aesthetic purpose, while active prostheses help amputees to perform bimanual tasks through their grasping functions. The body-powered active prostheses (Figure 1.2C) are controlled through a harness and cable system worn on the shoulder, while the electrically powered active prostheses can be controlled by brain-machine interface (Katyal et al., 2014; Lange et al., 2016), peripheral interface (Ciancio et al., 2016; Irwin et al., 2016; Thompson et al., 2016) or electromyographic signals (i.e. Myoelectric prosthesis, Figure 1.2D).




*1.2* ***Upper extremity amputation levels and prostheses types.*** *A) Representation of amputation levels (adapted from Cordella et al. (2016)). B) Cosmetic prosthesis. C) Body-powered (kinematic) prosthesis. D) Myoelectric prosthesis.*

Myoelectric prostheses are the most commonly used because of their ease of use. These prostheses adopt superficial electromyographic (sEMG) electrodes to record the muscle activities on the skin surface. Although this type of control suffers from crosstalk and is sensitive to electrode displacement and contact condition changes, it is still preferred by all commercial prosthetic providers because, unlike intramuscular EMG (iEMG), it is non-invasive. The methods for controlling myoelectric prosthetic can be divided into non-pattern recognition based methods and pattern recognition based methods. The non-pattern recognition control is used for prosthesis with 1 DoF. By recording muscle flexion activity to close and muscle extension activity to open the prosthetic hand, it is used for both on-off or proportional control. Pattern recognition based control, using phantom arm/hand movements, is the most promising control method that could be used to provide a good and useful replacement for the hand.

## 1.1. Phantom limb sensations

In 1871 S. Weir Mitchell coined the term “Phantom Limb” to describe the persisting sensory awareness of a limb after amputation (Katz, 1993; Mitchell, 1871). This sensory awareness, or sensation, is present immediately after the effect of the anesthetic or the pain relievers ends. About 90% of amputees reports phantom limb sensations (Giummarra et al., 2010; Richardson et al., 2018; Stankevicius et al., 2021) feeling different kind of sensations such as pain, touch, pressure, and temperature. Moreover, many amputees (about 50% according to Giummarra et al. (2010)) also report movement sensations, both voluntary and involuntary movements, of a phantom limb (Pirowska et al., 2014).

In the next chapters, I will explore the phantom arm sensations in detail from many different aspects. Perhaps because the syndrome was regarded as a clinical curiosity, many studies in the twentieth century reported phantom limb based on patient reports (Ramachandran and Hirstein, 1998). In neurology, many different clinical pathologies have been studied using qualitative reports from patients and it is only in the last decades that these “clinical curiosity” have been studied with quantitative methodologies. But in a sense, these qualitative reports were the doors that opened the possibility to study them and the interesting by the entire, scientific and not, community. The qualitative reports are the basis of the quantitative analyses, without which it could be difficult to find what we need to study; after all, the law of gravity was found thanks to the observation of a falling apple. For this reason, here I report some first-person reports by amputees describing how they discovered having a phantom arm/hand. These reports were collected during a period in the INAIL prosthetic center of Vigorso di Budrio (BO, Italy) where amputees can obtain or repair their prosthesis.

The names are not the real ones.

H.K. “I was at a cocktail bar, I was doing a happy hour with a friend, I remember feeling my hand itching between the thumb and the index, so I scratched myself. At that moment I realized that I was scratching my prosthesis, that was the first time I felt my phantom hand.”

L.S. “The first time I perceived the phantom hand was when I had the accident” *(at work)*. “My arm was inside the machine” *(he had and amputation for trauma on work, and the arm was inside a machine)*, “I tried to move the muscles. I do not know why I was not collapsed, I tried to do it to check whether the hand was intact. I knew that this was not possible. I saw the blood on my arm, it was impossible that inside the machine my arm was intact, but I remember feeling that I could move the fingers, maybe it was because the adrenaline”.

P.Q. “I do not know what is exactly the first time I perceived the phantom hand” *(he said phantom with a different voice)* “To me this is not a phantom, it is a real hand... or better... it is the soul of my prosthesis, without it my prosthesis is an empty object”.

T.S. *(This patient said this the second time we met for the experiments)* “After we met the first time, I started to train my *(phantom)* hand, now I can move every single *(phantom)* finger. This may seem very strange... I feel like if I can grasp the object with the *(phantom)* hand. I have to see the object, keep my eyes on it. I approach the object with my hand and in my mind it is as if I can grasp it” *(this was said watching an object that was on the table and he did the movement approaching the stump close to object but not touching it with the stump).*

C.I. “Often I gesticulate with my phantom hand, it is part of me. Now, while we are talking, I am gesticulating with it, I use it *(to gesticulate)* with my other hand. Of course, you cannot see it but for me it is real... Maybe because I am Italian.”

These subjective reports provide an intuition of how real phantom hand sensations are. While amputees perceive the phantom hand in different ways, they all feel that something not visible is (still) present. The reading of these reports helps us to better understand why it is so important to study phantom arm movements and sensations and the impact of this research on people’s life.

## 1.2. Phantom limb sensations and prosthesis embodiment

Phantom limb sensation, by definition, relate to the missing limb. However, perhaps unsurprisingly, they also influence how the prosthesis is perceived, and more specifically, the perception of the prosthesis as embodied.

As introduced in this chapter the prosthesis is the tool that try to replace the functionality of the missing hand, but its usability is related with the sensation that it is experienced like a real limb. When a tool is strongly connected with the body perception it can be defined embodied (Tsakiris et al., 2013). Embodiment occurs when an external tool enables the individuals to perceive and process information as they were elaborated by one’s body parts, thus processing the stimuli not only in their sensory or motor components but also at the affective level (de Vignemont, 2011). Relatedly, prosthesis is embodied when it is cognitively integrated with the amputee’s body representation (Makin et al., 2017). Prosthesis embodiment is reported by amputees as a key feature of prosthesis rehabilitation (Murray, 2009) and this importance is supported also by the experts working in the prosthetic rehabilitation field (Schaffalitzky et al., 2012). Nevertheless the quality of prosthesis embodiment is highly variable between amputees (Bekrater-Bodmann, 2020; Fritsch et al., 2021) Recent evidence suggests that the quality of prosthesis integration is related to different advantageous outcomes of prosthetic use, such as a better ability to judge the space of action around the prosthetic hand (Gouzien et al., 2017), a higher prosthesis satisfaction

(Bekrater-Bodmann, 2021) and a less intensity perception of phantom limb pain (Bekrater-Bodmann et al., 2021; Kern et al., 2009). The level of prosthesis embodiment is related to different predictors, such as the level of amputation, the time from amputation, the frequency of prosthetic use, the properties and complexity of prosthetic limb and, particularly relevant for the purposes of the present thesis, the sensation of the phantom limb (Bekrater-Bodmann, 2021, 2022; Bekrater-Bodmann et al., 2021; de Vignemont, 2011; Lotze et al., 1999; Murray, 2009).

Recent evidence suggests that the perception of the prosthesis can be influenced by phantom limb sensations. In upper limb amputees, qualitative interviews suggest that phantom limb experience can be positive, when phantom limb helps to control prosthesis, but also negative, when the patient reports that it is not possible to control the prosthesis because of the movement of the phantom limb (Bouffard et al., 2012). Moreover, some upper and lower prosthesis limb users report that their phantom perceptually joins the prosthesis (Giummarra et al., 2010). Recent quantitative analysis suggests that when the phantom limb is co-located in the prosthetic limb, the phantom can animate it, contributing to the cognitive integration of the prosthesis into the amputees' body representation (Bekrater-Bodmann, 2022; Saetta et al., 2021).

Finally it has also been reported that when phantom limb is coherently stimulated during prosthetic touch feedback, not only the prosthetic hand can be better embodied, but also the phantom arm can be perceived with a structure more similar to the intact one (Rognini et al., 2019).

These findings suggest a strong reciprocal influence between phantom limb and prosthesis embodiment that need to be explore to improve post-amputation rehabilitation and prosthetic use.

## 1.3. Thesis goal and organization

In recent decades, the study of phantom limb has attracted considerable interest from researchers with diverse background, from neural engineering to cognitive neuroscience and experimental psychology. This is unsurprising considering the multi-dimensionality of phantom limb sensations.

The goal of this PhD thesis is to develop a novel conceptual and experimental quantitative framework to investigate phantom arm/hand sensations. Specifically, the purpose of this thesis is two-fold. First, the thesis aims to review what is currently known (and not known) about phantom arm and hand movements. Second, the thesis aims to develop novel approaches to investigate multi-dimensional phantom sensations by combining various techniques including behavioral analysis, motion capture, and sEMG recordings. I anticipate that this thesis could help to pose new research questions in both the neuroscience and the prosthetic field.

Below I highlight the specific questions addressed in each chapter:

Chapter 2 reviews what is currently known on phantom arm movements at three different levels: kinematic level, muscle level and cortical level. This chapter is intended to provide an overview of the studies that investigated phantom arm movements at each of these levels. The interim conclusion from this literature review is that phantom arm/hand movements are governed by the same mechanisms that govern the intact arm movements.

Chapter 3 outlines a study which used psychomorphometry to explore how the phantom arm/hand is represented. In this study, I applied this quantitative technique to reconstruct the phantom arm/hand in a 2-dimensional space and investigate how the structure of phantom arm/arm changes across tasks.

Chapter 4 reports on a series of experiments aimed at expanding our knowledge of electromyographic properties of phantom arm movements. In particular, the studies aimed at i) exploring the specific spatial pattern activity of residual muscles during phantom movements, ii) analyzing how the specific pattern of muscles activity can change after amputation; iii) defining a new phantom arm training protocol to improve the specificity of muscles activity pattern related to each specific phantom movement.

Chapter 5 outlines a study which explored spatial coupling effects using a bimanual interference task. The aim of this study was to measure phantom kinematics and provide a rigorous test of the hypothesis that phantom arm movements constrain intact arm movements at the kinematic level.

Finally, Chapter 6 summarizes the findings of the present thesis and discusses open questions and future directions.

*"The phantom represents our normal experience of the body (. . .) it is the body we always feel, but without the input that normally modulates the central neural processes that produce the experience"*

*Melzack, 1989*

# 2. Chapter 2: And yet it moves: what we currently know about phantom arm movements

The results of Chapter 2 were published in "The Neuroscientist":

Scaliti, E., Gruppioni, E., & Becchio C. (2020). And Yet It Moves: What We Currently Know about Phantom Arm Movements. *The Neuroscientist 26* (4), 328-342.

## 2.1. Introduction

In his "Philosophical Investigation", Wittgenstein asks the question: "What is left over if I subtract the fact that my arm goes up from the fact that I raise my arm?" (Wittgenstein, 1953). Neurological evidence invites the provocative hypothesis that what is left over is a phantom arm movement – a movement of the arm where there is no physical component because the arm has been amputated. There are certainly questions around this phenomenon: what is it to move a phantom arm? (Vesey, 1961). What is it like to move a part of the body known to be gone? This review paper deals with these questions at three levels:

- the kinematic level: the evolution in time of the phantom joint angles and phantom hand configuration;
- the muscle level: the pattern of electromyographic (EMG) activity in arm muscles associated with phantom arm movements;
- the cortical level: the cortical representation of phantom arm movements.

We begin by outlining the phenomenology of phantom arm movements. We then discuss recent computational and neurobiological insights arising from attention to the properties of phantom arm and hand movements at each of the proposed levels – kinematic, muscle and cortical (see Table 2.1). We posit that phantom arm/hand movements are best conceptualized as real movements of a dematerialized arm/hand. Finally, we identify some challenges for future investigations and conclude by discussing some of the implications of this conception for prosthetic control. The review focuses on phantom arm and hand movements; we will not discuss phantom movements in lower limb amputees.

### *2.1* ***Studies investigating phantom movements divided at the three different levels: kinematic, muscle and cortical.***

| Level of description | Study | Aims | Technique | Paradigm | Results |
|---|---|---|---|---|---|
| Kinematic | | | | | |
| | De Graaf et al. (2016) | Quantify phantom movement kinematics and relate these to intact limb kinematics | Behavioral (cyber glove) | Synchronous imitation of finger F/E, precision grip and hand movements | *Executed phantom movements are slower and smaller in amplitude than intact limb movements.* |
| | Franz and Ramachandran (1998) | Test whether phantom movements reflect the operation of neural mechanisms that govern normal motor performance | Behavioral (tablet) | Spatial coupling paradigm | *Spatial coupling effects are reported in amputees with movable phantom, but not in amputees with immobilized phantom.* |
| | Garbarini et al. (2018) | Analyze inter-manual transfer from phantom to intact limb | Behavioral (cyber glove) | Inter-manual transfer of sequence learning; fingers-thumb opposition sequence | *Inter-manual transfer of sequence learning is reported after phantom limb training. Inter-manual transfer effects are not observed in amputees with immobilized phantom.* |
| Muscle | | | | | |
| | Cipriani et al. (2011) | Analyze online classification accuracy of phantom limb movements | sEMG | Execution of finger F, thumb opposition, tridigital grip, lateral grip | *Online decoding of phantom movements with an array of electrodes placed over the residual forearm yields an accuracy of 79% in transradial amputees (n=7).* |
| | Dhillon et al. (2004) | Analyze whether motor pathways associated with a missing limb remain functionally intact after nerve transection injury | LIFEs recording proximal nerve stump | n.a. | *Voluntary movements of the phantom limb generate activity in severed motor nerve fibers within the stump.* |

| | | | | |
|---|---|---|---|---|
| Hahne et al. (2018) | Test a regression-based control approach that allowed for simultaneous and proportional prosthetic control | sEMG | Execution of wrist F/E, wrist pronation/supination and little finger F | *Regression-based control outperforms conventional control in tasks mimicking daily life activities* |
| Jarrassé et al. (2017) | Test the involvement of stump muscles in phantom limb movements | sEMG | Execution of cyclic movement of F/E of single finger, hand O/C, pinch O/C, wrist F/E, wrist P/S, radial inclination, ulnar inclination, elbow F/E | *Online classification of phantom movements of elbow, wrist and hand yields an overall accuracy of approximately 70% in transhumeral amputees (n=14).* |
| Jarrassé et al. (2018) | Evaluate the possibility to use a phantom limb movements based control approach to perform more realistic functional grasping tasks | sEMG | Execution of elbow F/E, wrist P/S, hand O/C, pinch O/C | *Two transhumeral amputees used different phantom movements to reach, grasp and release three different objects (i.e cylinder, ball, clothespin) with a unworn eight-active-DoF prosthetic arm. The pattern recognition algorithm accuracy was above 80% for both amputees.* |
| Powell and Thakor (2013) | Test if training with pattern recognition algorithm is possible to improve muscle patterns during phantom movements | sEMG | Execution of 8 phantom movements for 5 seconds: Hand O/C, index pointing, fine pinch, Forearm P/S, wrist F/E | *10 days training with pattern recognition algorithm improve consistency and distinguishability muscle patterns of different phantom movements.* |
| Reilly et al. (2006) | Test whether the sensation of making a range of distinct phantom limb movements arises from distinct activity patterns in stump muscles | sEMG | Execution of cyclic movements of elbow F/E, hand O/C, wrist F/E, thumb F/E, and finger abduction and adduction | *Distinct phantom limb movements are associated with distinct patterns of EMG activity in stump muscles. Ischemic block reduces or eliminates the ability to move the phantom limb voluntarily and produces a dramatic reduction in the amplitude of stump muscle EMG activity.* |

| | | | | | |
|---|---|---|---|---|---|
| Cortical | | | | | |
| | Bestmann et al. (2006) | Investigate the neural correlates of TMS-induced conscious phantom movements | TMS + fMRI | n.a. | *Activity in a range of motor hand-related brain regions, including left (stimulated) M1, left and right PMd, left aIPS and caudal SMA, is greater on trials when a phantom movement is reported, than on trials when no phantom movement is reported.* |
| | Bruno et al. (2019) | Investigate inhibition of phantom limb movements | EEG | Go-NoGo task | *Suppressing intact and phantom limb movements evokes comparable inhibitory ERP responses* |
| | Cohen et al. (1991) | Elicit phantom limb movements with an artificial stimulation of the motor cortex | TMS | n.a. | *Magnetic scalp stimulation induces a sensation of movement of the missing hand in patients with acquired amputations, but not in a patient with congenital absence of the hand.* |
| | Hahamy et al. (2017) | Analyze changes in activation in amputees missing hand cortical territory | fMRI | Execution of cyclic movements of fingers F/E, elbow F/E | *Residual arms, lips and feet activate the missing hand territory in the sensorimotor cortex. The body parts that activate the missing-hand territory are those exceedingly used by one-handers to complete everyday tasks.* |
| | Kikkert et al. (2016) | Investigate changes in activity and digit topography in S1 after amputation | fMRI | Execution of individual digit movements | *Activity patterns in S1 show characteristic topography of the missing hand.* |
| | Mercier et al. (2006) | Investigate whether M1 maintains a hand representation after cortical reorganization | TMS | n.a. | *Stimulation of the hand region in M1 elicits phantom hand movements, including phantom limb movements that patients can no longer voluntarily produce. The topography of evoked phantom digit movements is highly systematic.* |
| | Raffin et al. (2012b) | Compare neural correlate of real and imagery phantom limb and intact limb movements | fMRI | Execution of hand O/C | *Phantom limb movements activate brain regions activate during execution of intact limb movements (M1, S1, SMA, the dorsal premotor cortex, cerebellum). Executed and imagined phantom and intact movements activate partially overlapping networks.* |

| | | | | |
|---|---|---|---|---|
| Walsh et al. (2015) | Investigate brain activity during preparation and execution of voluntary phantom limb movements | EEG | Keypresses (Libet paradigm) | *Phantom limb movements show classic EEG signatures of both the positive volition required to initiate action, and of the negative volition required to inhibit an action that is about to be performed.* |
| Wesselink et al. (2019) | Investigate whether persistent representation of a missing hand is present even in amputees with little phantom sensations. | fMRI | Execution of individual digit movements | *Hand representation in S1 in amputees with diverse phantom sensations is stable in amputees experiencing limited phantom sensations.* |

Note. LIFEs: longitudinal intrafascicular electrodes. sEMG: superficial electromyography. TMS: Transcranial Magnetic Stimulation. EEG: electroencephalography. fMRI: functional Magnetic Resonance Imaging. F/E: flexion and extension. O/C: opening and closing. P/S: pronation/supination. M1: primary motor-cortex. S1: primary somatosensory cortex. SMA: Supplementary motor area. n.a.: not applicable.

## 2.2. The phenomenology of phantom limb movements

Amputees commonly experience the feeling that the missing limb is still present; such feelings are accompanied by specific phantom sensations such as pain, touch, pressure, and temperature (Flor et al., 2006). Many amputees (about 50% according to Giummarra et al. (2010)) also report movement sensations from both voluntary and involuntary movements of a phantom limb (Pirowska et al., 2014). Commonly reported voluntary movements of the phantom arm/hand include reaching out to grab an object, making a fist, and moving one or more fingers individually (Ramachandran and Hirstein, 1998). The experience of involuntary phantom movements in response to external cues is also common. The phantom arm may fend off a blow, break a fall, or reach for a falling object (Reilly and Sirigu, 2008). Patients also report reflexive movements, such as the phantom hand suddenly moving to a new position or developing a clenching spasm (Ramachandran and Hirstein, 1998).

Since phantom movements are unobservable to bystanders, researchers in the 19th century originally attributed these to delusional sensations (Mitchell, 1871). Phantom limb movements, however, are not accompanied by delusional beliefs. Unlike patients with anosognosia for hemiplegia (e.g., Fotopoulou et al. (2008)), amputees do not deny the loss of their limbs. On the contrary, they know and visually perceive that the limb is missing. The experience of movement nevertheless persists, often accompanied by the distinct perception that the joints of the missing limb have moved (Anderson, 2018). Strikingly, this perception is not associated with imagined movements of the phantom arm, which suggests that amputees are capable of both executing a movement with their phantom arm and imagining the execution of a movement with their phantom arm (Raffin et al., 2012a).

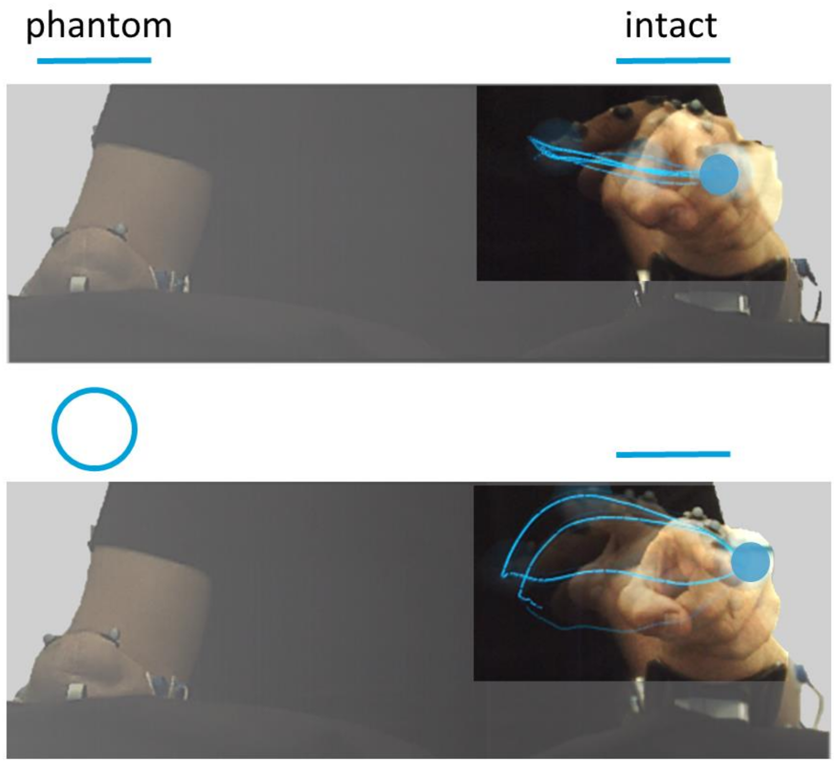
## 2.3. The *kinematics* of phantom limb movements

While the kinematics of phantom arm/hand movements cannot be tracked directly, phantom kinematics may be measured indirectly. One approach is to ask patients to mimic the phantom movements synchronously with the intact limb. De Graaf et al. (2016), for example, used a Cyber glove to measure the kinematics of the intact limbs of eight upper/forearm arm amputees who had been instructed to mimic phantom limb movements, such as opening and closing the hand, and flexion and extension of the wrist and fingers. As in a number of previous reports (Gagné et al., 2009; Raffin et al., 2012b; Reilly et al., 2006), mimicked movements were generally slow and small in amplitude. The relative time for execution of flexion/extension, and opening/closing movements were nevertheless preserved, with extension of the wrist and finger opening being faster than wrist flexion and fin- ger closure movements. Some patients reported experiencing the feeling of the phantom hand being “bound” or “restrained in a tube” as fatigue increased.

The mimic-with-the-intact-limb approach relies on two assumptions: first, that the intact hand mimics the movement of the phantom hand; and second, that the movement of the intact hand does not influence the movement of the phantom hand. The second assumption is clearly not true for intact bilateral movements, which reveal strong inter- limb coupling effects (e.g., Franz et al. (1991)).

A second approach reverses the logic of the mimic- with-the-intact-limb approach, taking advantage of inter-limb coordination to capture assimilation effects between an intact hand and a phantom hand. Under typical movement conditions, asking a subject to draw lines with one hand while concurrently drawing circles with the other hand results in spatial assimilation between the two limbs, with each shape becoming more elliptical com- pared with when both hands produce lines or circles (Franz et al., 1991; Pia et al., 2013). This spatial assimilation effect is thought to reflect interhemispheric interactions between cortically based spatial coding (Ivry et al., 2004). Franz and Ramachandran (1998) capitalized on this effect to investigate bimanual coupling in amputees. Line-circle drawing revealed that volitional phantom arm movements imposed spatial constraints comparable to those evident in control participants performing movements with two intact limbs (Figure 2.1). Amputees with immobilized phantom limbs, in contrast, showed no coupling effects. Furthermore, evidence of spatial coupling was absent in control participants producing actual movements with one limb while vividly imagining movements of the other limb, suggesting that the effect is specific to executed movements.

Using similar logic, studies have reported inter-manual transfer of motor skills from a phantom to an intact limb. In non-amputees, training one limb enhances the performance of the contralateral, untrained limb (Perez et al., 2007a; Perez et al., 2007b). Garbarini et al. (2018) observed an analogous transfer effect in an amputee trained to perform finger-thumb opposition sequences with her phantom hand. After phantom hand training, the patient was faster and made fewer errors per- forming the sequence with her intact, untrained hand. No transfer effect occurred when training involved imagined phantom movements (Garbarini et al., 2018). Collectively, these findings provide evidence for crosstalk between intact and phantom hand movements and suggest that bimanual coordination patterns extend to phantom limb movements. Correspondingly, the lack of crosstalk when using imagined phantom movements indicates that there is no functional equivalence, and thus no coordination, between executed and imagined phan- tom limb movements.

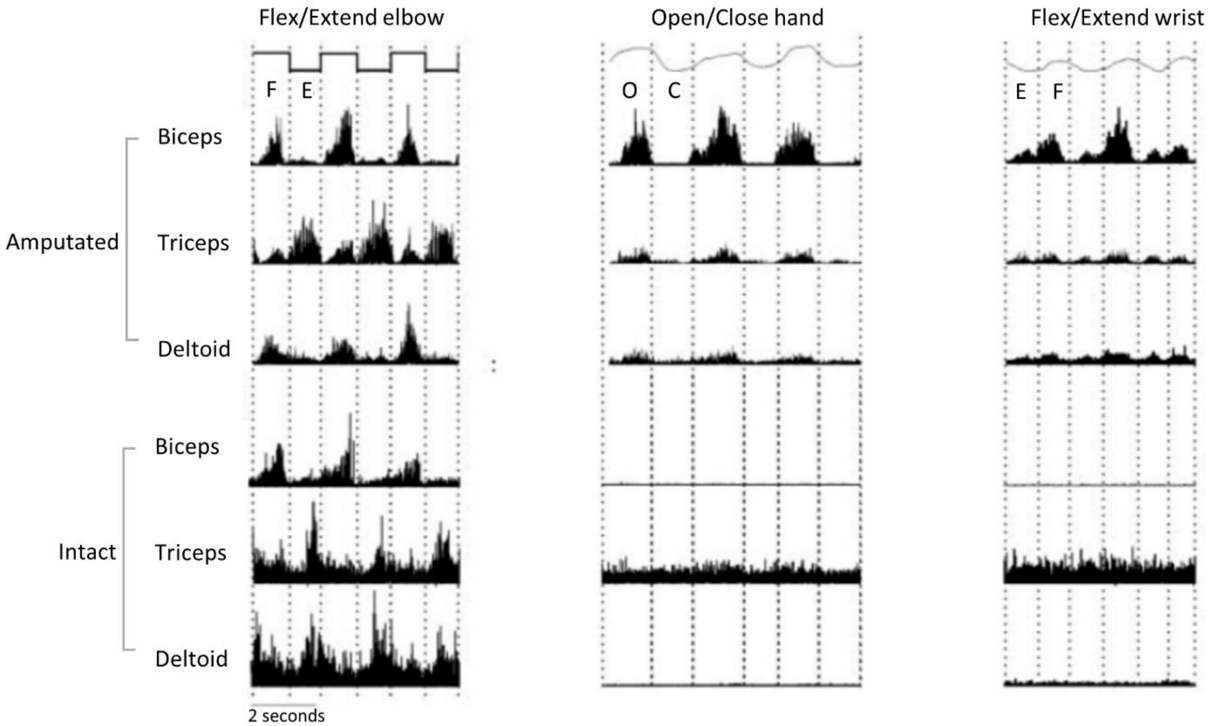



*2.1.* ***Spatial assimilation effect in an amputee with phantom hand.*** *Drawing lines with the intact hand while concurrently drawing circles with the phantom hand results in spatial assimilation, with lines drawn with the intact hand becoming more elliptical (lower panel) compared with those produced when both hands—intact and phantom—draw lines (upper panel). Cognition, Motion, and Neuroscience Lab at the Italian Institute of Technology.*

Following similar logic, other studies have reported inter-manual transfer of motor skills from a phantom to an intact limb. Training one limb enhances the performance of the contralateral, untrained limb (Perez et al., 2007a; Perez et al., 2007b). Garbarini et al. (2018) observed an analogous transfer effect in an amputee who had been trained to perform finger-thumb opposition sequences with her phantom hand. After phantom training, the patient was faster and made fewer errors performing the sequence with her intact, untrained hand. The transfer was not observed when the training involved imagined phantom movements (Garbarini et al., 2018). These findings can be collectively interpreted as evidence for crosstalk between intact and phantom hand movements, suggesting that bimanual coordination patterns extend to phantom limb movements. Correspondingly, the lack of crosstalk with imagined phantom movements reinforces the notion that there is no functional equivalence, and thus no coordination, between executed and imagined phantom movements.

## 2.4. The *Electromyography* of phantom limb movements

Consistent with the kinematic evidence indicating phantom movement are executed and not just imagined, reports indicate that voluntary (but not imagined) movements of the phantom evoke patterns of activity of stump muscles. This activity does not simply reflect random contractions of stump muscles but instead is movement-specific; distinct phantom movements are associated with distinct movement-related patterns of EMG activity (Reilly et al., 2006). Phantom movement EMG patterns remain stable over time and can be reproduced across multiple testing sessions, sometimes with months between sessions (Reilly et al., 2006). This may indicate that pre-amputation EMG patterns are maintained, except the stump muscles involved in phantom movements are not the same muscles that are ordinarily involved in intact hand movements (Reilly et al., 2006). For example, Reilly et al. (2006) reported unexpected activation of biceps, triceps, deltoid and brachialis muscles during phantom hand movements. The co-activation pattern in these muscles varied across subjects and movements. Figure 2.2 shows EMG recordings of intact and stump muscles for patient RR in Reilly et al. (2006). The patient executed three distinct cyclic bilateral movements: elbow flexion/extension, hand opening/closing and wrist flexion/extension. Flexing and extending the phantom limb was associated with an alternating triphasic pattern of EMG bursts in agonist and antagonist muscles. This pattern was similar to that observed for flexion and extension of the intact elbow. In contrast, during hand opening and closing and wrist flexion and extension, a co-activation pattern occurred with simultaneous EMG bursts in biceps, triceps and deltoid muscles for phantom limb movements. This was not the case for intact limb movements; intact hand and wrist movements revealed no phasic modulation of biceps and triceps.

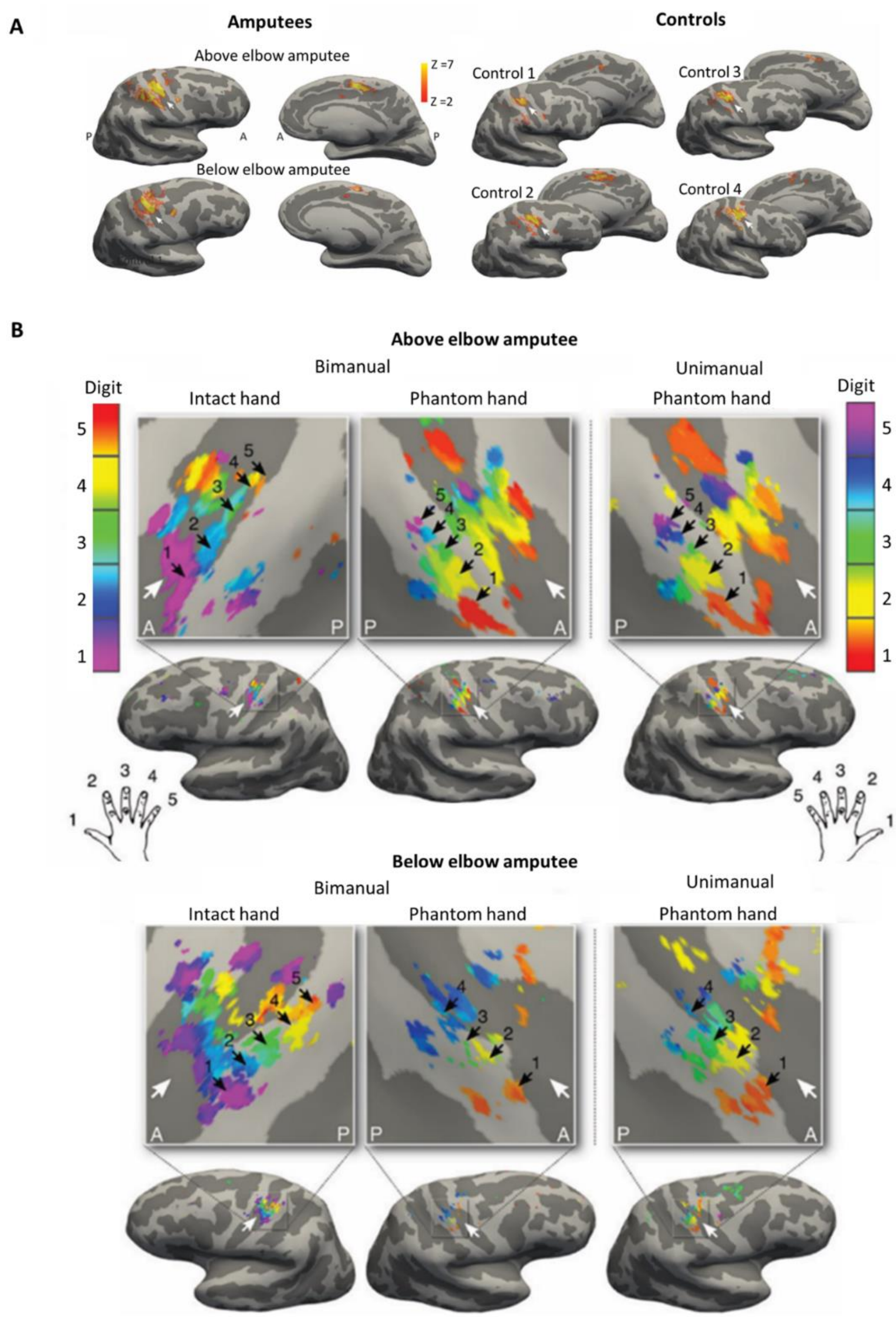



*2.2.* ***Electromyography (EMG) of phantom movements.*** *Raw EMG profiles of an amputee executing three distinct cyclic bilateral movements. Adapted from Reilly et al. (2006). Note: O = opening; C = closing; F = flexion; E = extension.*

Together, these results suggest that EMG activity related to phantom limbs results from a retargeting of stump muscles rather than from maintaining pre-amputation patterns. It is not entirely clear how this retargeting takes place. After amputation, spinal motor neurons either undergo retrograde degeneration or find new muscle targets. In turn, the corticospinal neurons that synapsed with the degenerated motor neurons must find new motor neuron targets. Those remaining connected to motor neurons that have changed muscle targets will influence an altered the set of muscles (Levine, 2007). The EMG pattern for phantom movements could reflect this peripheral reorganization. Alternatively, post-amputation EMG patterns may result from a restructuring the central connectivity of the neurons in the hand areas of motor and sensory cortex. The next section reviews neuroimaging studies designed to consider this possibility.

## 2.5. The cortical representation of phantom limb movements

In the mammalian brain, primary sensorimotor cortices are topographically organized so that neural activity relating to adjacent body parts is mapped onto anatomically adjacent cortical sites (Penfield and Boldrey, 1937). An historically influential hypothesis suggests that following hand amputation, cortical neighbors (i.e., the lips) take over the "freed up" hand territory (Flor et al., 2006). Support for this hypothesis stems from functional magnetic resonance imaging (fMRI) studies showing a shift of cortical representation from neighboring areas of the somatosensory and motor maps to the deafferented cortical representation (e.g., Maclver et al. (2008)). During lip pursing, for example, amputees had abnormal activations extending into the contralateral M1 arm/hand area. These studies used lip stimulation or lip movement to investigate cortical reorganization. This approach is suitable for documenting shifted representation of cortical neighbors. However, it fails to explore the possibility that the brain "remembers" the amputated hand: The original hand function could be preserved in the cortical territory for the amputated hand (Merzenich et al., 1984). Support for this hypothesis comes from imaging studies showing comparable patterns of movement-related activity when amputees move their phantom hands relative to two-handed controls moving their non-dominant hands (Bestmann et al., 2006; Kikkert et al., 2018; Makin et al., 2013) (Figure 2.3A). The digit topography of phantom hand movements and intact hand movements are strikingly similar. By employing ultra-high-field neuroimaging to uncover single digit representations of the missing hand, Kikkert et al. (2016) found that individual finger representation persists in the primary somatosensory cortex of amputees decades after amputation (Figure 2.3B). These amputees experienced vivid phantom sensations (Kikkert et al., 2016). Wesselink et al. (2019) extended this work to show persistent digit representations among amputees who experienced few phantom sensations. The authors measured cortical hand representation in 18 acquired amputees with varying levels of phantom sensations and in 13 individuals missing one hand from birth owing to congenital amelia. Representational dis- similarity analysis for individual digit patterns revealed similar inter-digit organization in controls and acquired amputees, including amputees with little to no kinesthetic sensations. In contrast, congenital one-handers showed no differentiation among digits of the missing hand. Together, these results suggest that cortical reorganization does not abolish original hand representation and that peripheral input is necessary to establish—but not to maintain—such representation.




*2.3.* ***Patterns of neural activity during single digit phantom and intact movements.*** *(A) Amputees and controls show similar patterns of movement-related activity in the primary somatosensory and motor cortex (left hemisphere), as well as in the supplementary motor area* *(right hemisphere). (B) Distinct intact and phantom hand representations in amputees performing single digit flexion and extension movements in a traveling wave paradigm. The paradigm involves paired simultaneous digit movements of the intact and phantom hands (bimanual) and unimanual digit movements of the phantom hand (unilateral). Maps contralateral to the missing hand in the bimanual task resemble missing hand unimanual maps. White arrows indicate the central sulcus. Adapted from Kikkert et al. (2016). Note: A = anterior; P = posterior.*

## 2.6. The principles of cortical reorganization

The finding that missing hand topography can co-occur with remapping of body parts raises the question of whether missing and intact limb representations coextend within the same cortical territory. Related to this, is whether such representations are functionally orthogonal or interact (Andoh et al., 2018). Studies that leverage transcranial magnetic stimulation (TMS) to directly stimulate the motor cortex (M1) of amputees (e.g., Mercier et al. (2006); Reilly et al. (2006)) have reported significant overlap in stimulation sites that evoke phantom movements and those that evoke responses in stump muscles. This may suggest that representation of the missing hand and the expanded representation of stump muscles coexist in the same cortical territory. Whether cohabitation within the amputated hand territory extend to other body parts remains controversial. Using surface-based cortical distance analysis of fMRI data, Makin et al. (2015) identified consistent shifts in lip representation contralateral to the missing hand toward, but not invading, the hand area. In that study, hand cortex activity during lip movements did not correlate with chronic phantom limb pain, challenging the assumed link between reorganization and phantom limb pain (see 2.6.1).

One factor that might explain the discrepancies across studies are compensatory behavioral strategies (Hahamy et al., 2015; Makin et al., 2013). Compensatory behavior can involve multiple body parts (e.g., stump, lips), including body parts distant from a missing hand (e.g., feet). Using fMRI to measure brain responses of people born with one hand, Hahamy et al.

(2017) found that large-scale cortical reorganization shows diversified compensatory profiles; among participants, body parts used to complete everyday tasks showed increased representation in the cortical territory for the missing hand. This could indicate that, at least in congenital one-handers, reorganization at a cortical level is not restricted topologically to cortical neighbors and can extend to any body part mimicking the missing hand functionality.

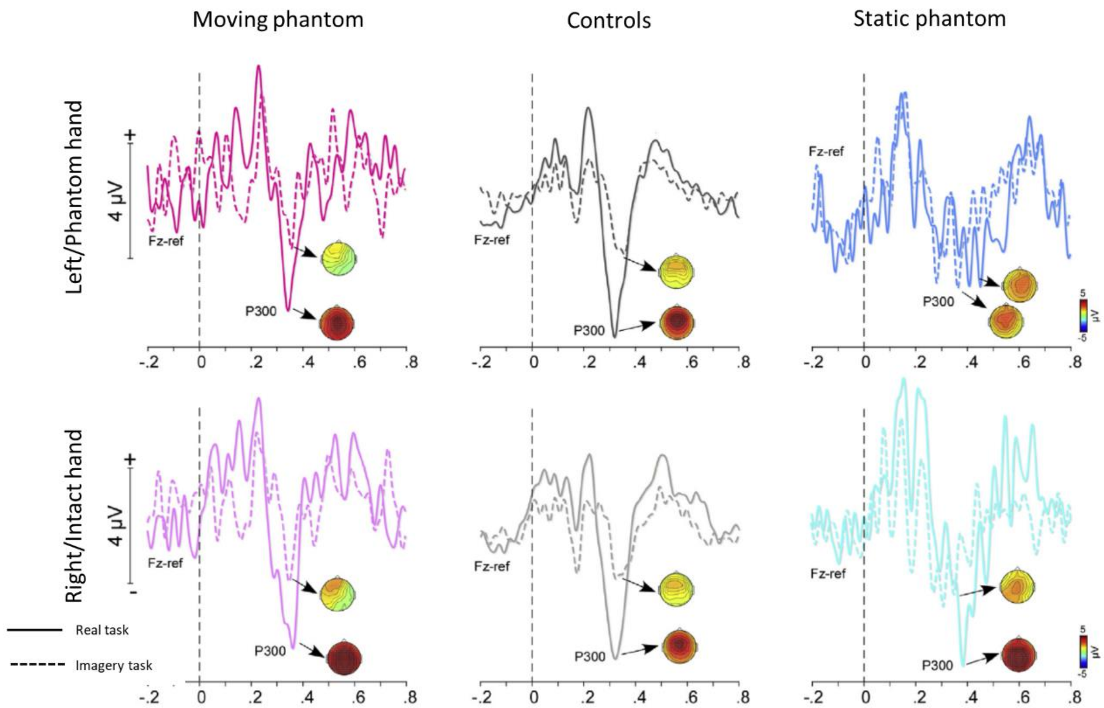
### 2.6.1. Treating phantom pain with phantom movement

A variety of behavioral therapies use phantom movements to relieve painful sensations perceived as originating from the missing limb (Moseley, 2006; Ortiz-Catalan et al., 2016; Raffin et al., 2016; Ramachandran and RogersRamachandran, 1996). In phantom limb motor execution intervention, for example, phantom limb movements are decoded using myoelectric pattern recognition, while providing real-time visual feedback via virtual and augmented reality (Ortiz-Catalan, 2018). Other training protocols focus on improving phantom limb motor output using visual and tactile feedback (De Nunzio et al., 2018). Although training of phantom limb movements reduces phantom limb pain in amputees with chronic intractable phantom limb pain (e.g., Ortiz-Catalan et al. (2016), the mechanisms of this pain reduction are not well understood. One hypothesized mechanism is a *reversal of cortical reorganization*, whereby training of phantom movements purposefully reengages the missing limb hand neural circuitry, counteracting maladaptive cortical plasticity following amputation (e.g., Flor et al. (1995); Karl et al. (2001); Lotze et al. (2001); Raffin et al. (2016)). This mechanism is in keeping with studies reporting a positive correlation between the severity of phantom limb pain and degree of cortical reorganization (e.g. Raffin et al. (2016)). Other studies, however, suggest phantom limb pain sensations are associated with preserved, though less functionally connected, representation of the original hand (e.g., Kikkert et al. (2018); Makin et al. (2013)). Thus, *increased functional inter-regional connectivity* is another possible mechanism explaining pain reduction related to phantom limb movement. Finally, training phantom limb movements has been hypothesized to disentangle pain processing circuitry through *competitive plasticity*. This latter mechanism refers to the idea that reengaging the missing limb circuitry in movement execution can prevent its engagement in pain processing.

(This part is not present in the original text of the published article) Further studies may deepen the concept of reorganization. This is particularly true for the maladaptive theory that is based mostly on correlation data; relatedly, Makin (2021) suggests not to infer causation from a correlation. It is also important to note that many different approaches were developed to treat phantom pain, but all of them were always referred to the mirror box mechanism developed by Ramachandran and Rogers-Ramachandran in 1996. For this reason, it is difficult for new approaches to find fertile ground to posit new insight in phantom limb treatment. This could be really useful since although researches found strong effective with this mirror box based approaches these are not always effective and give not us the possibility to answer why amputated people perceived this pain and how it is originated (Makin, 2021). Thus, we need to think outside the mirror box to find new potentially more successful treatments (Makin, 2021).

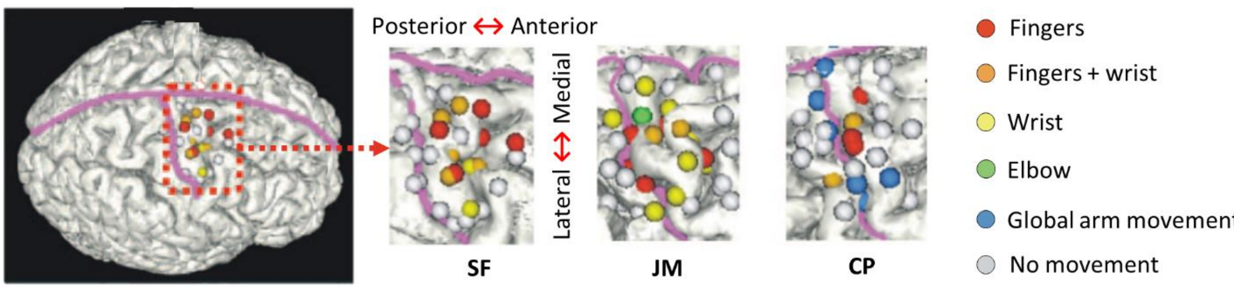
## 2.7. Linking levels: Inaccessible phantom movements and induced paralysis

Some amputees cannot generate voluntary phantom limb movement (Ramachandran and Hirstein, 1998). Others lose this ability as time passes, with the range of motion and number of movements decreasing as time since amputation increases (Ramachandran, 1993). The mechanisms behind an inability, or loss of ability, for voluntary phantom limb movement remain poorly understood. In amputees who can move phantom limbs, electroencephalography (EEG) markers typically associated with voluntary actions accompany the preparation of voluntary action in the phantom limb: a pre-movement event- related desynchronization in the alpha and beta bands, followed by a post-movement beta rebound (Walsh et al., 2015). EEG activity during voluntary inhibition of phantom limb movements also resembles that of intact movements (Walsh et al., 2015). Bruno et al. (2019) found that amputees with a static (i.e., paralyzed) phantom limb do not show classical motor-inhibition related EEG patterns (Figure 2.4).



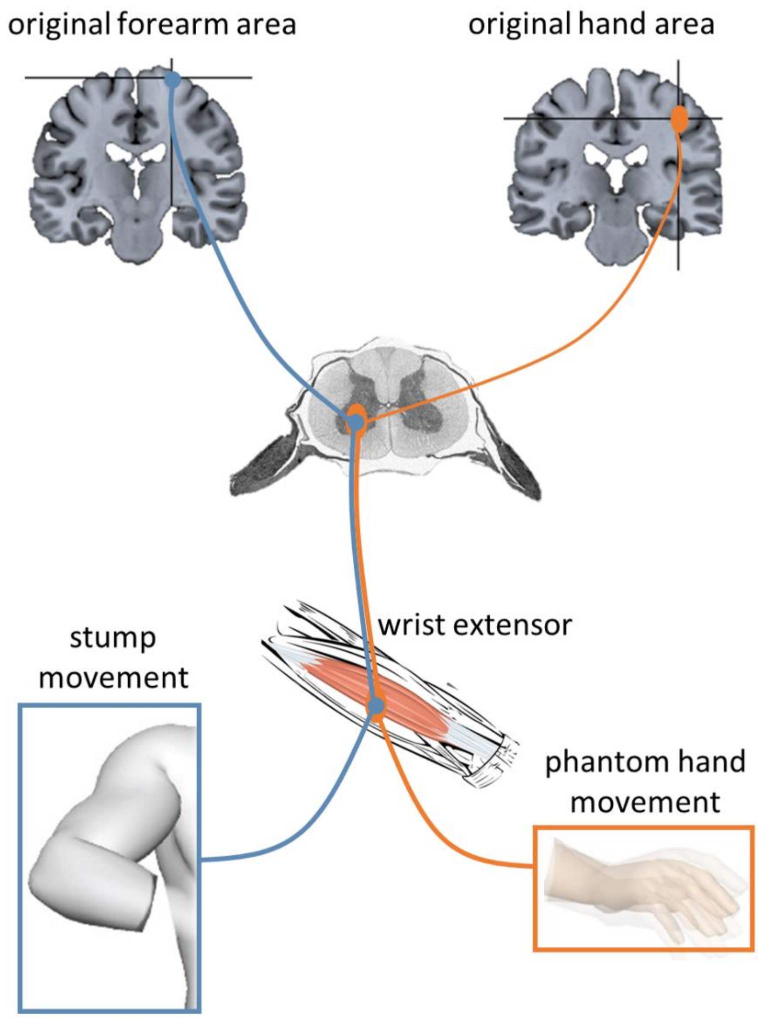

*2.4.* ***Event-related potential (ERP) grand average waveforms on Nogo trials for an amputee with moving phantom arm, controls, and an amputee with static phantom arm.*** *ERPs were collected while participants performed a real (solid lines) or imaginary (dashed lines) Go/Nogo task with the left/phantom hand (upper part) or with the right/intact hand (lower part). The amplitude of the Nogo-P300—interpreted as reflecting response inhibitory processes—was similar for the amputee with a moving phantom hand and controls. The amputee with a static phantom hand showed a reduced Nogo-P300 similar in amplitude to the Nogo-P300 for controls in the imaginary task. Data are displayed in microvolts as a function of time post-cue onset for the Fz electrode (referenced to the nose). Adapted from Bruno et al. (2019).*

This, however, does not necessarily indicate that their wrist or elbow motor representation has faded away. Mercier et al. (2006) found that phantom limb movement that amputees could no longer voluntarily produce could be triggered by TMS over the contralateral missing-hand area (Figure 2.5). This suggests that phantom movement paralysis does not necessarily reflect a loss of movement representations, but rather it reflects inaccessibility to volitional control. However, how phantom limb representations are voluntarily accessed and how TMS might contribute to reawakening voluntarily inaccessible phantom limb movements remains unclear (Mercier et al., 2006).




*2.5.* ***Transcranial magnetic stimulation–evoked phantom movement in three amputees.*** *Stimulation sites evoking movement perceptions are concentrated on the anterior part of the central sulcus, over the primary motor cortex. Movement at different phantom joints, including joints for which voluntary movement are impossible, can be evoked at different stimulation sites (represented with different colors). The inter-hemispheric fissure and the central sulcus are traced in purple. Adapted from Mercier et al. (2006).*

The contribution of afferent feedback arising from contractions elicited in the stump muscles likewise remains unclear. Reilly et al. (2006) found that induction of an ischemic block via inflation of a blood pressure cuff around the elbow reduced or eliminated the amputee's ability to move the phantom hand. This result suggests that motor commands must arrive at the selected stump muscles and generate ascending afferent sensory feedback for the amputee to experience movement in the phantom limb (see also Jones (1988)). A working hypothesis is that phantom movement sensations arise at the interplay between efferent information and afferent feedback with efferent motor commands used to interpret afferent feedback (Mercier et al., 2006). For example, if a motor command arises from the stump area, the brain interprets the resulting afferent feedback from wrist extensor contraction as a stump movement. If the motor command arises from the original hand area, then the brain might interpret the same wrist extensor contraction as phantom hand movement (Figure 2.6). This hypothesis is consistent with the idea that the primary motor cortex contributes to sensory processing of afferent feedback during kinesthetic illusory limb movements (Naito, 2004).

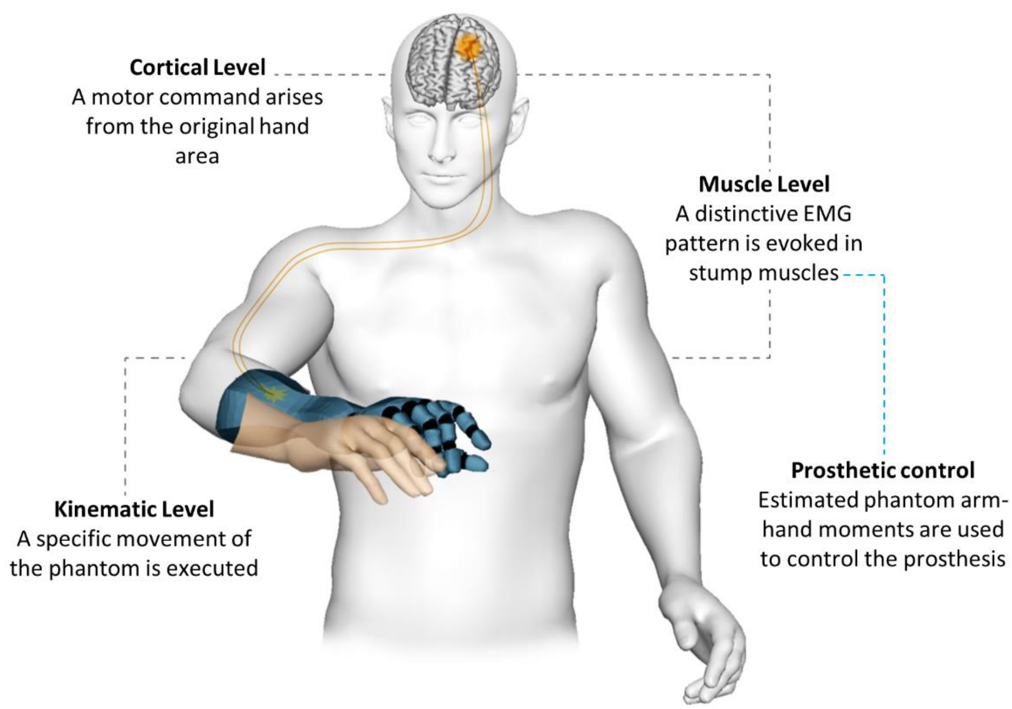



*2.6.* ***Origins of phantom movements.*** *A working hypothesis is that phantom movements originate at the interface between afferent and efferent signals. When the efferent motor command arises from the original forearm area (in blue), the brain interprets the afferent feedback from wrist extensor contraction as a movement of the stump. In contrast, when the* *motor command arises from the original hand area (in orange), the brain interprets the same afferent feedback from wrist extensor contraction as a movement of the phantom hand.*

## 2.8. Phantom arm movements as real movements of a dematerialized arm

The view that phantom limb sensations, such as phantom pain, are not real has long been dismissed. Even so, traces of epiphenomenalism continue to surround the concept of phantom limb movement. Some authors have reported that amputees experience the illusion that they can generate movements with their phantom arm (e.g., Ramachandran and Hirstein (1998)). This implies that phantom limb movements are little more than motor illusions. Evidence reviewed here clearly indicates that phantom movement sensations are not illusions. The illusion of movement, such as that induced by the vibration of muscle tendons, is created by the crossing of afferent visual and proprioceptive signals in the absence of efferent motor commands (Jones, 1988). In contrast, phantom arm movements are generated by specific arm/hand motor commands—motor commands that persist over time and, in the absence of constraints (ischemic block), lead to distinctive EMG patterns. The resulting movement paths, while not directly observable, can be observed through their effect on the kinematics of the intact hand. Taken together, these findings suggest that, at kinematic, muscle and cortical levels, phantom arm movements reflect the operation of the same mechanisms governing execution of intact hand/arm movements. Such a conclusion marks a shift in the conceptualization of phantom limb movements, from illusion of movement to real movement of a dematerialized arm/hand. However, more research is needed to determine the sequence of operations across kinematic, muscle, and cortical levels that lead to the generation of phantom movements.

In another direction, it is important for future studies to explore the implications of phantom arm movements for prosthetic control. When training for pattern recognition control, it is common practice to encourage amputees to use their phantom arms to control prostheses (e.g., Simon et al. (2012)). The conditions under which phantom movements are useful nevertheless remain unclear. Research on phantom arm/hand movements could help articulate these conditions. We anticipate that the increasing appreciation of phantom limb movements as real, executed movements will provide insight for developing new training strategies and prosthesis control methods (see 2.8.1), as well as for the embodiment of prosthetic devices (Niedernhuber et al., 2018; Pazzaglia and Molinari, 2016). Combined with intuitive bio- mimetic human-machine interfaces (e.g., Sartori et al. (2018)), this approach could ultimately lead to closing the motor control loop, and thereby materialize phantom limb movements into an artificial limb that interacts with the external world (see Figure 2.7) and conveys touch percepts back to its wearer (see 2.8.2).

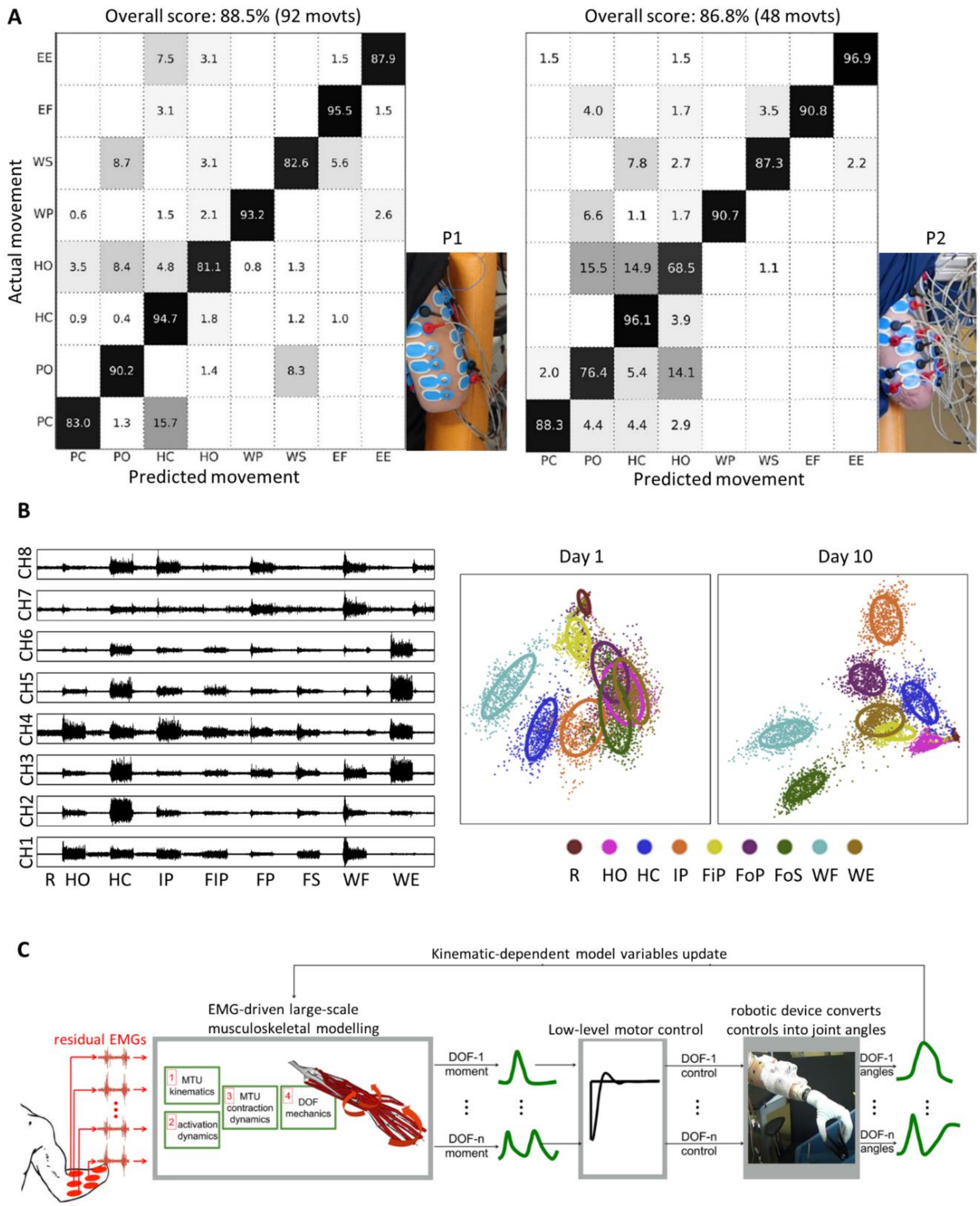



*2.7.* ***Potential of phantom arm movement for prosthetic control.*** *Schematic illustrating the potential use of phantom movement for controlling a prosthesis. During execution of a phantom limb movement (pictured as the transparent hand displaced from the body), activation of the specific hand motor command leads to a distinctive pattern of electromyographic (EMG) activity. A model-based decoder translates the phantom-related EMG pattern into movement of the prosthesis. In this way, the prosthesis materializes the intended phantom limb movement.*

*The dashed gray line indicates the descending pathway responsible for the execution of phantom movements. The dashed blue line indicates the interface between phantom limb movement and prosthetic control.*

### 2.8.1. Pattern recognition of phantom movements

State-of-the-art myoelectric control for multifunction upper limb prostheses is based on EMG pattern recognition (Resnik et al., 2018). In training for pattern recognition control, EMG activity recorded from the residual limb is used to train an algorithm to recognize which muscles are contracting and to what degree during a given movement (e.g., hand open). Once trained, the pattern recognition system monitors the user's muscle contractions and uses this information to estimate what movement the user is attempting to perform. Although studies do not always mention it, a common way of feeding pattern- recognition myoelectric control in clinical practice is to collect EMG signals during phantom limb movements. In a study designed to formally test the possibility of using surface myoelectric activities of residual limb muscles associated with phantom limb movements for prosthetic control, (Jarrassé et al., 2017) found that classification of 14 phantom movements of elbow, wrist, and hand yielded an overall accuracy of approximately 70%. Similarly, Cipriani et al. (2011) reported an accuracy of 79% when decoding seven finger movements with an array of electrodes placed over the residual forearm (see also Jarrassé et al. (2018)). Jarrassé et al. (2018), asked two above-elbow amputees to perform different phantom movements in order to control a robotic arm and reach-to-grasp three different objects (cylinder, ball, and clothespin); the overall accuracy of the algorithm was above 80% for both patients (see Figure 2.8A). Amputees in these studies received no training in mobilizing phantom limbs. Powell and Thakor (2013) report that user training implementing visual biofeedback from a virtual prosthesis improved both the consistency and distinguishability of phantom limb movements (Figure 2.8B). Such results highlight the potential of phantom limb movements as a means of developing new training strategies. Going one step further, Sartori et al. (2018) recently demonstrated the potential of phantom wrist-hand movement for real-time prosthesis control using an EMG- driven musculoskeletal modeling approach (see Figure 2.8C). Using this approach in conjunction with high-density electromyograms (HD-EMG), the authors were able to estimate four-degree of freedom (DOF) arm mechanics based on accurate EMG-driven simulations of phantom limb movement (Sartori et al., 2019).




2.8. **Decoding of phantom arm/hand movement from electromyographic (EMG) activity.** *Voluntary movement in phantom hand, wrist and elbow can be decoded using multi-electrode* *arrays and pattern recognition algorithms. (A) Confusion matrix for decoding of eight phantom movements performed by two transhumeral amputees (P1 and P2) with mobile phantom limbs. Electrode placement is shown for each patient. Adapted from Jarrassé et al. (2018). (B) (Left) EMG signals obtained from eight electrode channels during the execution of eight phantom movements. (Right) Two-dimensional projections of a high- dimensional EMG dataset from a transradial amputee at day 1 and day 10 of pattern recognition training. Axes are on an arbitrary scale and ellipses delimit the region containing the most data points for each movement. Adapted from Powell and Thakor (2013). (C) Model-based control schematics for myoelectric robotic limbs. A musculoskeletal model predicts the muscle forces of residual forearm muscles as well the resulting joint moments acting on the amputee's phantom limb. EMG-decoded joint moments are then converted into prosthesis low-level motor commands. Adapted from Sartori et al. (2018). EE = elbow extension; EF = elbow flexion; WP = wrist pronation; WS = wrist supination; PO = pinch open; PC = pinch close; R = rest; HO = hand open; HC = hand close; IP = index point; FiP = fine pinch; FoP = forearm pronation; FoS = forearm supination; WF = wrist flexion; WE = wrist extension; MTU = muscle-tendon unit; DOF = degrees of freedom.*

### 2.8.2. Closing the loop

Haptic signals, especially from contact events, are essential for skilled and dexterous object manipulation. For example, when grasping and lifting an object, signals from tactile afferents provide information on both the timing and the physical nature of the discrete mechanical events that occur when the digits contact the object (Flanagan et al., 2006). The feasibility of artificially providing object-related tactile information to upper limb amputees via peripheral nerve stimulation was first demonstrated in an early prosthetic implementation in 1974 (Clippinger et al., 1974). Sensation elicited with single channel cuff electrodes was perceived on the phantom limb, but it was generally a diffuse, unstable sensation, described as paresthesia. Following this first attempt, a number of studies have reported on the possibility of closing the control loop of prostheses using peripheral nerve stimulation to elicit intuitive touch percepts (e.g., Graczyk et al. (2016); Mastinu et al. (2019); Raspopovic et al. (2014); Tan et al. (2014); for review, see Pasluosta et al. (2018)). The challenge of providing a completely natural sensory experience persists (Ortiz-Catalan, 2018). Ideally, successful sensory feedback in a prosthesis would not only restore motor function (i.e., control of forces during manipulation or object recognizing during exploration), but also induce embodiment (Pasluosta et al., 2018). In line with this, Schiefer et al. (2016) found that stimulation of peripheral nerves with extraneural cuff-type electrodes on residual nerves in upper limb loss amputees improved not only fine control of a myoelectric prosthesis but also embodiment of the prosthesis and confidence.

(This part is not present in the original text of the published article) By combining multisensory visuo-tactile neural stimulation and transverse intrafascicular multichannel electrodes, Rognini et al. (2019) found that tactile stimulation administered with coherent visual feedback can induce prosthesis embodiment and reduce the telescoping effect in amputees with upper limb amputation. These results speak to the importance of solutions to close the loop and integrate the prosthetic hand with phantom limb in order to deliver both motor and tactile information.

*"A patient describing this condition (the phantom arm sensation) insisted that the stump felt far less distinctly present than the hand, which, for him, appeared to lie in the stump, save that the finger-ends projected beyond it."*

*S. Weir Mitchell 1871*

# 3. Chapter 3: The structural properties of phantom arm

## 3.1. Introduction

Evidence discussed in Chapter 2 suggests that phantom arm movement are best conceptualized as real movements of a dematerialized, invisible hand. This requires a stored representation of the phantom arm/hand. The study presented in this chapter aimed at addressing the metric properties of phantom body parts and how they are represented in external space.

Some patients localize the "invisible" limb in the position previously occupied by the amputated hand/arm. However, other patients localize it in a different position. In particular, patients with an upper limb amputation often report a progressive shortening of the phantom arm, with the phantom hand shrinked closer or directly attached to the stump (i.e., telescoping phenomenon reported in 28-67% of patients; Giummarra et al. (2010); Jensen et al. (1985); Kuner and Flor (2017); Richardson et al. (2007); Weiss and Fishman (1963)). Previous studies described telescoping with qualitative methodology, that is, by interviewing patients on their telescoped or not phantom arm sensation. The present study aimed at providing a quantitative characterization of this phenomena. More generally, I was interested in developing a method to measure the phantom arm/hand and render it "visible". To do so, I extended the psychomorphometry method developed by Longo and Haggard (2010) to study the body metric properties of the phantom limb. In the original version of the task, participants lay their hands on a table underneath an occluding board and use a long baton to judge the location of the knuckle and tip of each finger. By comparing the relative judged location of each landmark, it is possible to derive a perceptual map of hand structure, which can then be compared with actual hand structure. These maps reveal systematic pattern of distortion. Specifically, across a number of studies, three characteristic patterns of distortions are apparent: underestimation of finger length (i.e., the distance between the knuckles and tip of the fingers), overestimation of the hand width (i.e., distance between pairs of knuckles), and a radial–ulnar gradient with underestimation of finger length increasing systematically from the thumb to the little finger (Ferre et al., 2013; Longo, 2014; Longo and Haggard, 2010, 2012; Longo et al., 2012; Lopez et al., 2012). In this study, I adapted this method to investigate whether and to what extent these patterns of distortion also apply to the phantom arm/hand.

## 3.2. Methods

### 3.2.1. Participants

Three individuals with acquired unilateral upper limb amputation (mean age ± standard deviation of the mean ± SD = 43 ± 13, two with absent right hand; Table 3.1) were recruited at the INAIL prosthetic center (Vigorso di Budrio (BO), Italy). All of them were transradial amputees (i.e. amputation below elbow). All participants provided written informed consent. The study conformed to the standard of the Declaration of Helsinki and was approved by the ethical committees of Bologna-Imola.

3.1 **Patients participating to structural properties study details.** Note: TR: Transradial amputee.

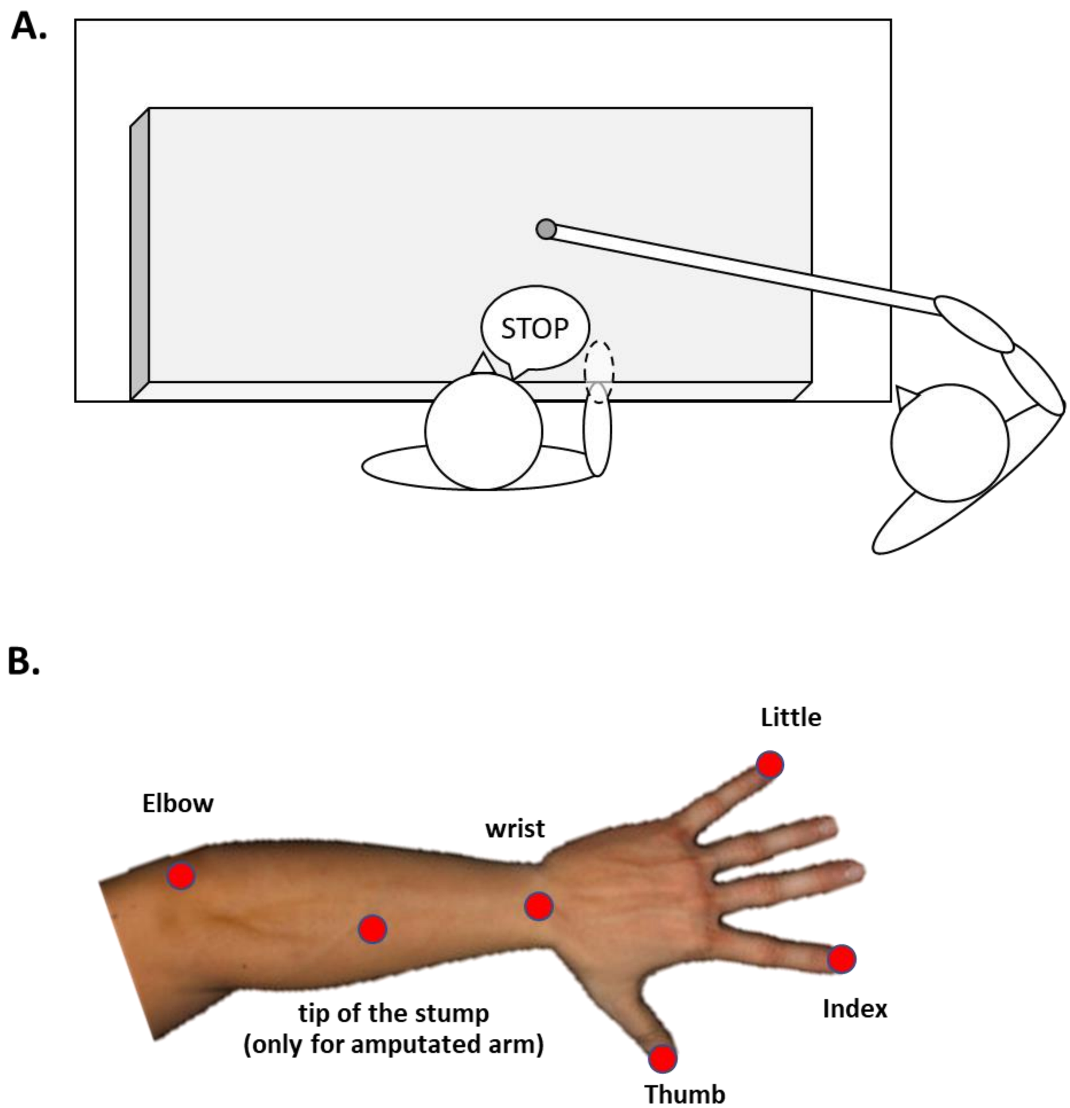
| *Patients* | *Age* | *Sex* | *Time since amputation (y)* | *Cause of amputation* | *Side / dominant* | *Daily prosthesis used* |
|---|---|---|---|---|---|---|
| *TR001* | 39 | F | 15 | Drive accident | L / R | Myoelectric |
| *TR002* | 57 | M | 25 | Trauma on work | R / R | Cosmetic / myoelectric |
| *TR003* | 32 | M | 5 | Trauma on work | R / R | Cosmetic / myoelectric |

### 3.2.2. Experimental procedure

In order to explore the psychomorphometry of the phantom arm, patients performed the Body-Landmarks localization task (Canzoneri et al., 2013). Patients sat on a comfortable chair with their either intact or stump arm, basing on task condition, placed on a table in a prone position. The forearm was aligned with the shoulder joint. During the task, arms were covered by a rectangular black box (70 cm long x 120 cm wide) to avoid participants to view it. The specific landmark to judge was verbally cued by the experimenter on each single trial. The experimenter moved the retro-reflective marker (1.5 cm in diameter), stacked on the tip of a white cane 100 cm long, randomly over the box. Participants were instructed to say “Stop” when the retro-reflective marker was perceived just above the felt position of the target anatomical landmark (Figure 3.1A). At that verbal signal, the experimenter ended the movement leaving the marker where indicated by the participant. The participant was allowed to further adjust the final position of the marker, by verbally asking the experimenter to move it backward or forward. When the participant confirmed the final position, the marker’s location was recorded through an optical motion capture system (Vicon system).

The actual position of each body landmarks was recorded on the intact arm, while the participants was blindfolded, placing retro-reflective markers on the anatomical landmarks. Participants were asked to judge landmarks position on phantom arm and intact arm in 2 different blocks. Landmarks selected were elbow joint (i.e. the lateral epicondyle), tip of stump (only for amputated arm), wrist (i.e. center between ulna and radius styloid), tip of little finger, tip of index finger and tip of thumb finger (Figure 3.1B). Each landmark was judged 5 times in a fully randomized order for a maximum of 30 trials per block.

After body-landmark task, patients performed the *active length estimation task*. Patients were asked to perform reach to tap movements with the phantom hand towards an object. The object consisted in a 3D printed plastic cube (dimension 3x3 cm) placed on a stand at the same high of the shoulder and distant 40cm from the middle line of the body. One retroreflective marker was placed on the center of top face of the cube and to patients were asked to touch it with the phantom tip index finger. Moreover, one retroreflective marker was placed on the tip of the stump. Patients were asked to say to the experimenter when they "touch" the object with the phantom index finger. They performed 5 trials in total.




*3.1 A) Body-landmark task representation. B) Body landmarks selected.*

### 3.2.3. Data analyses

A custom MatLab (Mathworks, Natick, MA) script was employed to analyze data. For the *Body landmark task,* the position of the marker for each trial was used to calculate the mean two-dimensional position of each perceived anatomical body landmark. Trials with a deviation standard higher than 1.5 or lower than -1.5 by the mean were excluded. Then, the two-dimensional Euclidian distance (1) between the specific perceived positions of the landmarks was calculated.

$$d(A,B) = \sqrt[2]{(x_1 - y_1)^2 + (x_2 - y_2)^2} \quad (1)$$

In particular, I calculated the distances between: the elbow and the tip of the sump (only in phantom condition), the elbow and the wrist, the wrist and the thumb, the wrist and the index and the wrist and the little. The length of each finger, as well as the related hand structure, was calculated from the wrist in order to exclude any confound related to the lower distance between elbow and wrist. All the distances were compared with the same real distances calculated using marker placed on the intact arm. The ratio Δr (2) between perceived phantom distances (PPD) and real intact distances (RID) was used to evaluate whether patient overestimate or underestimate the perceived phantom comparing with the intact arm distances.

$$\Delta r = \frac{PPD}{RID} \quad (2)$$

Moreover, the Δp (3) was calculated that was the ratio between the perceived phantom distances (PPD) and the perceived intact distances (PID) in order to control that there was not any perceived error.

$$\Delta p = \frac{PPD}{PID} \quad (3)$$

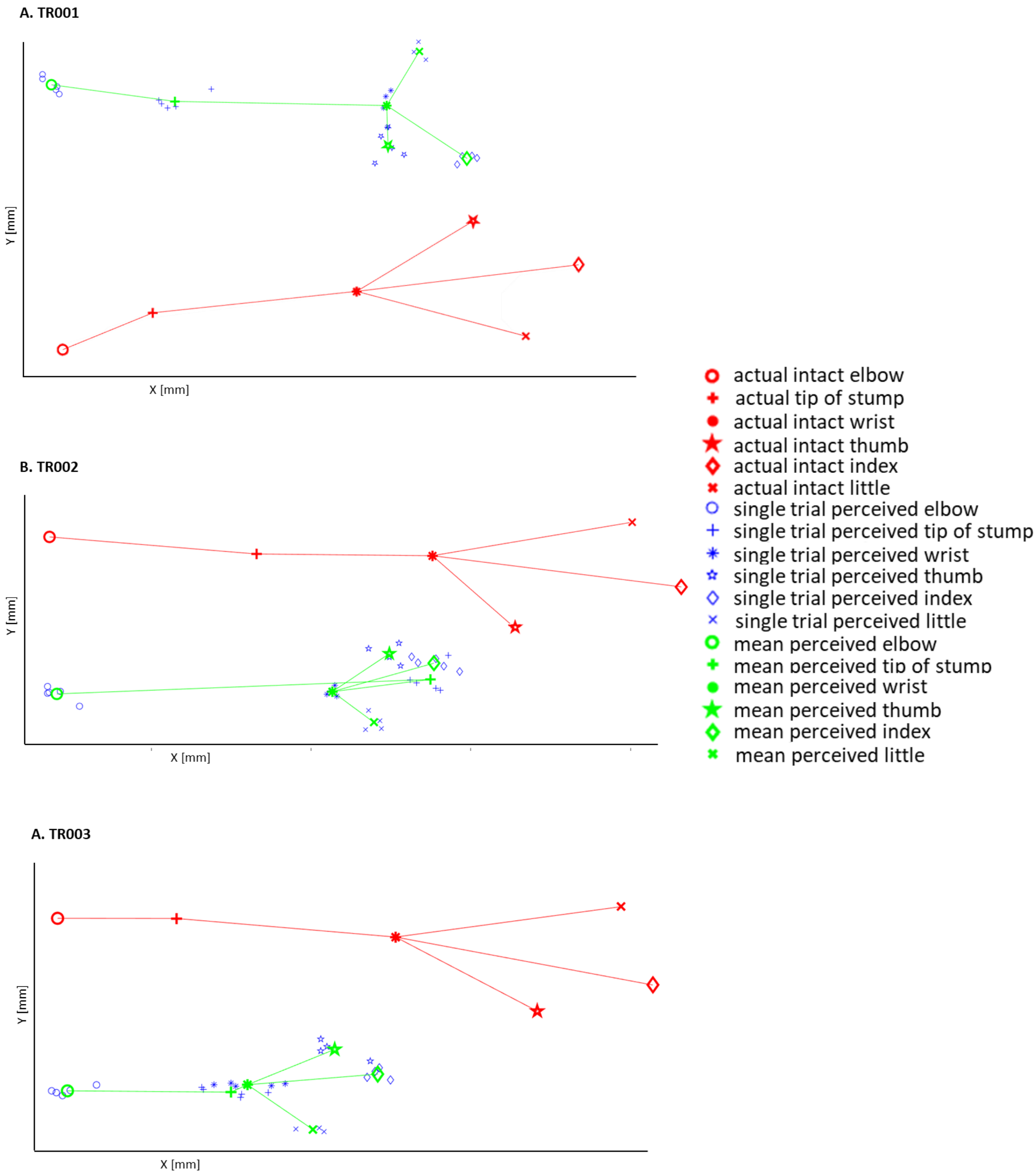
Values of Δ higher than 1 means an overestimation of the distance between landmarks compared to real or perceived intact structure, while lower than 1 an underestimation.

For the *active length estimation task*, the Euclidean distance (1) between the position of marker on the cube and the position of the marker on the stump was calculated for each trial. This distance was compared with i) the Euclidean distance calculated from body landmark task between the actual tip of the stump and the perceived tip of index finger and ii) with the actual distance calculated on the intact arm.

## 3.3. Results

### 3.3.1. Perceived structure of the phantom arm compared to the real structure of the intact arm

The results showed that, while each amputee perceived the phantom arm/hand in a different way, some distortions applied to all participants. In particular, patient TR001 did not show the telescoping effect, but the phantom hand was perceived smaller than the intact one (Figure 3.2A). Patient TR002 showed a strong telescoping effect; the length of the stump (i.e., the distance between the elbow and the tip of the stump) was overestimated, while the phantom wrist and hand were located inside the stump, with phantom fingers shorter than the real intact one (Figure 3.2B). Patient TR003 showed a telescoping effect with the phantom wrist directly attached to the stump (Figure 3.2C). In general, all the patients showed an overestimation of the length between the elbow and the tip of the stump and an underestimation of the length of the fingers (i.e. calculated between the wrist and the tip of each fingers, Figure 3.3A).

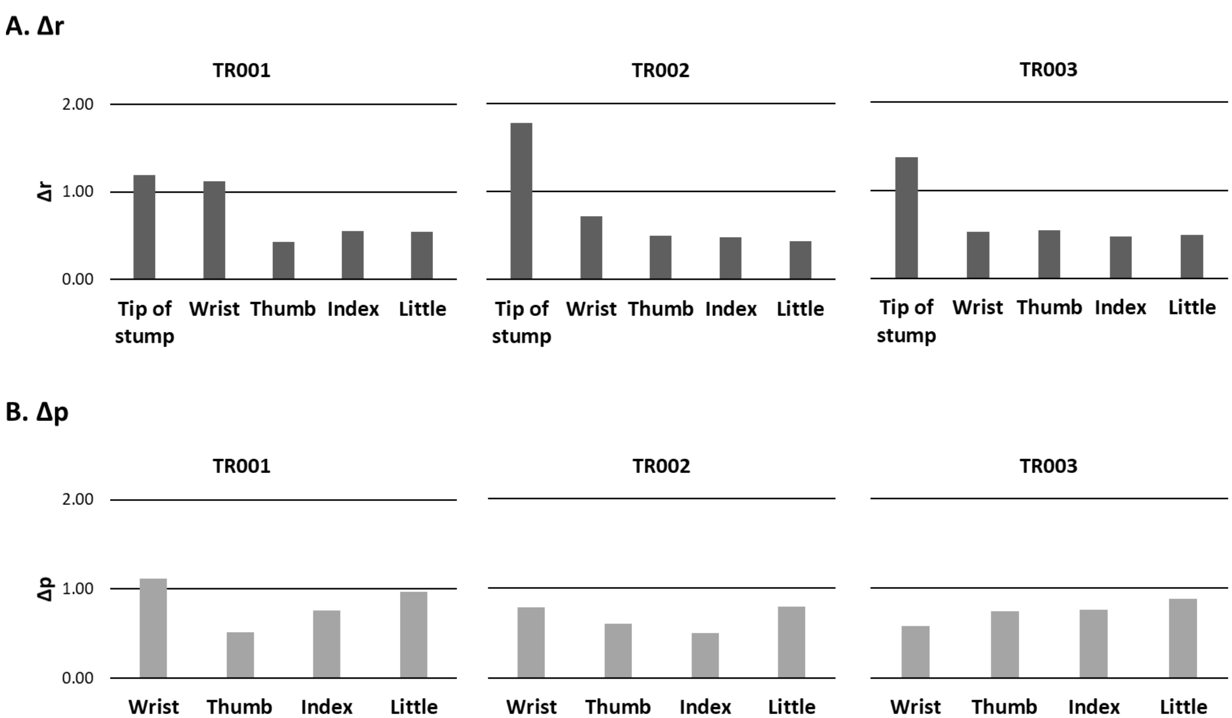



*3.2.* ***Perceived structure of phantom arm compared with real structure of intact arm.*** *In blue are represented the single trial for each different body landmarks. In green the mean across each single trial. In red the real structure of the intact arm.*

### 3.3.2. Perceived structure of the phantom arm compared to the perceived structure of the intact arm

As discussed above, numerous studies have revealed large and highly consistent distortions of body representations in healthy human adults (Ambroziak et al., 2018; Longo, 2017). To compare the distortions of the phantom with the ones of the intact limb, I also compared the perceived phantom hand with the perceived intact hand.

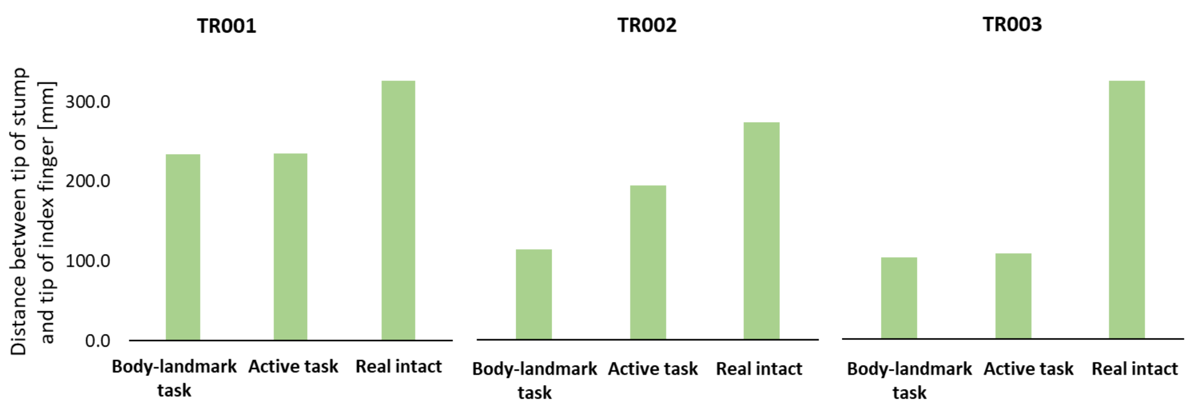
Results showed that, for each patient, the perceived phantom hand was shorter than the perceived intact one. Moreover, for patient TR002 and TR003 also the perceived distance in the phantom arm between elbow and the wrist was shorter than the perceived distance in the intact arm, showing that the telescoping effect was real. Differently this distance was not different in the patient TR001 that did not show the telescoping effect (Figure 3.3B).




*3.3.* ***Single patient results of body-landmark task.*** *A) comparison between perceived phantom arm structure and real intact arm structure (Δr). B) comparison between perceived phantom* *arm structure and perceived intact arm structure (Δp). Values equal to 1 represent no differences between the two structures compared.*

### 3.3.3. Structure of the phantom arm during the active task

For patients TR001 and TR003 the distance between the actual tip of the stump and the perceived index finger calculated with the body landmarks task was not different from the distance from the actual tip of the stump and the marker on the object that the patients were instructed to "tap" with the phantom index finger. In contrast, in patient TR002, the distance between the tip of the stump and the tip of the index finger increased during the active task. (Figure 3.4). This suggests that in patient TR002, the phantom hand, perceived as inside the stump, was displaced during active movement.




*3.4.* ***Single patient results of active length estimation task. D****istances between the tip of the stump and the tip of the index finger calculated from body-landmark task, active task and real structure of intact arm.*

## 3.4. Discussion

Results showed that phantom arm structure is specific and different for each patient.

Previous study on telescoping effect reported this phenomenon with qualitative methodologies (Bekrater-Bodmann et al., 2015; Flor et al., 2006; Richardson et al., 2015), moreover, they only investigated the distance between the stump and the phantom hand. In this study, I explored the telescoping effect with a quantitative methodology and how patients perceive the phantom hand, obtaining the phantom perceived arm structure.

The body-landmark task showed that in patient TR001, the length of the arm and in particular the distance between the elbow and the phantom wrist was similar to the intact one, while the phantom hand structure was shorter. In patient TR002, the phantom hand was inside the stump, but the stump length was overestimated compared to the actual length. Finally, TR003 perceived the phantom hand directly attached to stump showing a strong telescoping effect. Patient TR001 perceived distance between the elbow and tip of stump similar to the actual one, differently, patients TR002 and R003 perceived this distance longer and in TR002 the phantom hand was inside the perceived length of the stump.

Moreover, comparison between the perceived phantom arm and the perceived structure of the intact arm showed that phantom arm is underestimated, so shorter than the perceived intact one. The fact that the perceived structure of phantom arm is different from the perceived structure of the intact arm reveals that the phantom hand has specific structural properties and is not represented only as the real intact one. Moreover, findings by Sorrentino and colleagues (2021) suggested that the length of the dominant hand is underestimated compared to the non-dominant one (Sorrentino et al., 2021); here results showed that the length of the non-dominant amputated hand is underestimated compared to the dominant intact one, suggesting that the phantom structure perception is not related to dominance bias.

Finally, results of *active length estimation task* showed that during movements the phantom structure did not change in patient TR001 and TR003; differently, in patient TR002 the phantom hand displaced from the stump. It is possible to speculate that during phantom hand movements, in patients with the telescoped phantom hand inside the stump, it occupies a different space in order to “act” in the environment. Future studies, with larger number of patients, should explore whether this effect could be present in all the patients that perceived the phantom hand inside the stump. Moreover, future studies should explore the connection between phantom structure and prosthesis embodiment. As discussed in section 1.2, many patients report that the phantom arm can occupy the same space as the prosthesis. In a recent study Rognini et al. (2019), using a body landmark task similar to the one reported here, showed that, after prosthesis embodiment, the telescoping of the phantom was lower and that the finger were perceived in a more distal position, closer to the position of the intact fingers.

## 3.5. Limitations

The limit of the present study is represented by the number of patients recruited. Moreover, the differences between patients on phantom structure perception did not allow to perform statistical analyses. Next studies should improve the number of patients in order to lack these limitations.

*"A phantom limb is essential if an artificial limb is to be used"*

*Oliver Sacks, 1970*

# 4. Chapter 4: The electromyographic properties of phantom arm

## 4.1. Introduction

Control of active prostheses is via human-machine interfacing. The interfacing can be realized at the brain, peripheral nerve, or muscle level. Among these potential options, however, muscle interfacing is currently the only viable option for controlling external devices in commercial and clinical systems (Farina et al., 2014).

The EMG signal is a measure of the muscle generated electrical currents during contraction (Raez et al., 2006). Despite the fact that EMG recordings are peripheral measurements and are not obtained directly from neural cells, they contain neural information on the executed motor tasks (Farina et al., 2014). Recent studies described novel, non-invasive approaches to prosthetic control based on the placement of electrode arrays over the residual group of muscles and the implementation of pattern recognition based on multivariate decoding analysis. Pattern recognition-based control strategy has the potential to make control easier and more natural for prosthesis users. This strategy relies on machine learning algorithms to detect and classify EMG signals (Hakonen et al., 2015). Specifically, electromyographic signals recorded from the residual stump muscles are used to extract features for classification algorithms. These signals are typically segmented into time windows (generally of 200 ms) and used to calculate features such as mean absolute values (MAV), root mean square (RMS), zero-crossings (ZC), median frequency (MF). These extracted features are used then for classification algorithms such as linear discriminant analysis, artificial neural networks and support vector machines (Dellacasa

Bellingegni et al., 2017; Oskoei and Hu, 2008). Alternatively, regression-based myoelectric control approaches have been proposed (Farina et al., 2014).

Although not always mentioned, EMG interfacing is based on phantom limb movements. In a typical experiment, patients are asked to perform different phantom movements (e.g. elbow flexion, elbow extension, forearm pronation, forearm supination, wrist flexion, wrist extension, hand open, hand close) while wearing an sEMG array around their stump; classification results of these studies typically report accuracy higher than 75%. Moreover, Cipriani et al. (Cipriani et al., 2011) report that pattern recognition could classify fine movements of each single phantom digits in order to control polydigital hand prosthetics via decoding finger muscle activities with an array of electrodes placed over the stump. Powell and Thakor (2013) reported that using a training with pattern recognition is possible to improve phantom limb movement consistency and distinguishability. This kind of training could be useful in order to enhance the prosthesis control with pattern recognition.

Taken together, these findings suggest that pattern recognition approach based on phantom movements increase control possibilities in upper limb amputees and can give a more intuitive and natural way to control these prostheses with many different DoFs (Cipriani et al., 2011; Herberts et al., 1973; Jarrassé et al., 2018; Kristoffersen et al., 2020).

In general, researches in the last decades were affected by a lack in the connection between neuroscience, in terms of the study of generation of muscles activities due to phantom movements, and engineering, related to the implementation of complex pattern recognition algorithm in myoelectric prosthesis control. The studies reported here are attempted to combine two disciplines in order to better understand the mechanism related to phantom movements. In particular, this chapter reports of three studies analyzing different aspects of electromyographic activities during phantom arm movements.

The first study analyzed the specific spatial pattern activity of residual muscles during phantom movements and explored the possibility to use High Density surface Electromyography

(HDEMG) as a non-invasive methodology to decode a large number of phantom wrist/hand movements. Prostheses with more than two DoFs are promising new technology to restore upper limb lost ability after amputation. However, the control of these prostheses requires that muscles activity from more than two sources is recorded and analyzed. Invasive techniques, such as longitudinal intra-fascicular electrodes (LIFEs, Micera et al. (2011)), have shown some potential but problems such as infections and difficulty to replace components remain unaddressed. Building on recent studies that analyzed the spatial topography of muscle activity of HDEMG (Parajuli et al., 2019; Stango et al., 2015; Tuncer et al., 2020), in this study, I demonstrate the potential of HDEMG for decoding phantom hand and finger movements.

The second study aimed to compare movement classification based on EMG data between phantom and intact arm. Reilly et al. (2006) reported qualitatively that patterns of electromyographic activity during phantom movements are different from the ones during intact movements. Difference in EMG patterns between intact and phantom movements remained therefore largely unexplored. To overcome this limitations, I used an extension of the classification approach known as cross-classification (Cichy and Teng, 2017). Classification reveals statistical dependencies between movements and EMG activity but does not characterize the EMG representation further. To characterize the similarity between intact and phantom EMG representations, I first tested EMG patterns recorded from the stump and the intact arm for movement information. Next, I assigned the stump and the intact arm to the training and testing sets to test the extent to which phantom movements re-instantiated patterns similar to those of intact movements. If a classifier trained on EMG data from the stump successfully classifies EMG pattern recorded from the intact limb (high cross-classification accuracy), this would provide direct evidence that the EMG representations are similar across phantom and intact movements. Conversely, a drop in cross-classification accuracy would provide evidence that the two EMG representations are dissimilar.

The third study evaluates the effects of a 2-day phantom hand movement training protocol on phantom movement classification. As mentioned in chapter one the most used hand prostheses has 1 DoF and are controlled proportionally by wrist flexor and extensor muscles. Prostheses with more than one degree of freedoms are controlled switching between the different degrees of freedom sequentially using EMG trigger generated by muscle co-contractions (Kristoffersen et al., 2019). This type of control for more DoFs has an unintuitive nature that make prostheses movement difficult and cognitively complex (Kristoffersen et al., 2020). One of the most important challenge to combine pattern recognition algorithm with phantom arm movements is to make each specific phantom movement easy to distinguish from each other. For this reason, a specific training for phantom arm movements could be useful to improve the distinguishability between movements and their specific pattern of muscle activity.

All three studies used Linear Discriminant Analysis (LDA) to classify different phantom limb movements performed by amputees during specific experimental tasks. LDA is a linear algorithm that is ideally suited to perform classification into a discrete set of possibilities. It is simple and interpretable and, for this reason, it was preferred in this application to other approaches, such as support vector machines or regression methods (Ameri et al., 2014; Hahne et al., 2014; Ortiz-Catalan et al., 2014). Regression methods are more suited for the decoding and control of continuous variables. By using regression-based approach, it is possible to estimates a proportional activation for each DoF of the prosthesis and control each DoF independently, simultaneously and proportionally (Farina et al., 2014). This allows, for example, amputees to perform slow wrist rotation and fast hand opening simultaneously (Hahne et al., 2018). For these characteristics, this technique is best suited for real-time decoding of continuous variables. In the studies presented in this chapter, the analyses were conducted in order to map specific discrete movements and the movement decoding was off-line; for this reason, we adopted LDA to discriminate different phantom movements.

## 4.2. Study 1: High density maps of muscles activity during phantom wrist/hand movements

### 4.2.1. Materials and methods

#### *4.2.1.1. Participant*

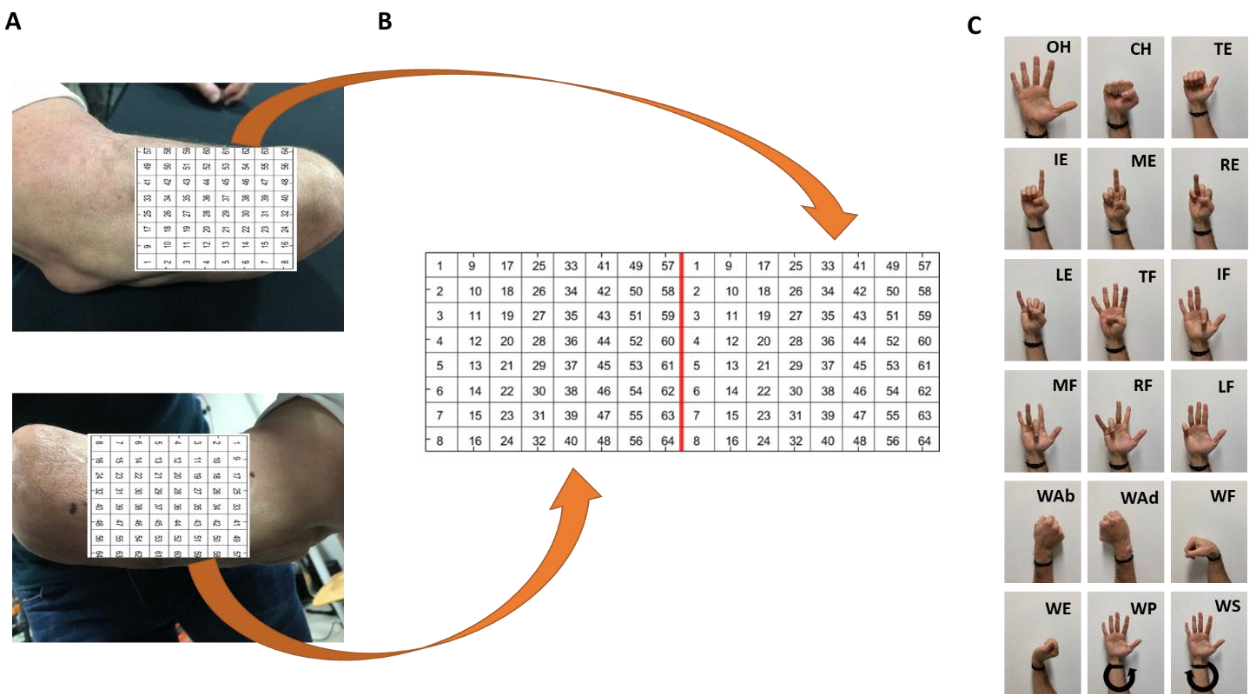
One individual with acquired right upper limb amputation (age: 57 years old) was recruited at the INAIL prosthetic center (Vigorso di Budrio (BO), Italy) and participated to the experiment. Amputation at a transradial level was caused by trauma related to a work accident and occurred 25 years before the recruitment. Participant provided written informed consent and the study conformed to the standard of the Declaration of Helsinki and was approved by the ethical committees of Bologna-Imola.

#### *4.2.1.2. Phantom movements rating*

Before starting the experiment, a semi-structured interview on prosthesis use and phantom limb sensation was conducted. The daily used prosthesis was a proportional myoelectric prosthesis worn for all day. Moreover, he owned a sport prosthesis used during volley matches. He reported that he started to feel phantom sensations around 1 week after the surgery. He never felt any referred touch sensation (i.e. touch sensation on phantom hand when touched on different stump, face or any body part). Phantom limb pain was not perceived during the days of experiment and in the last 1 week. Generally, when present, the pain was low (3/10 on a Visual Analogue Scale). Patient reported the ability to perform voluntary phantom wrist and hand movements; in particular, he reported he could perform with the phantom limb the 80% of movements performed with the intact one. He also reported the ability to perform single phantom finger movements (thumb: 80%, index: 80%, middle: 80%, ring: 80%, little: 75%). Finally, he said that phantom movements were effortless than intact ones and that phantom presence sensation was all-day present.

#### *4.2.1.3. Experimental protocol and task execution*

The patient was seated in a comfortable chair with his intact forearm and stump placed on a table (Figure 4.1A). He was asked to perform 18 different phantom wrist/hand movements in this specific order: open hand (OH), close hand (CH), thumb extension (TE), index extension (IE), middle extension (ME), ring extension (RE), little extension (LE), thumb flexion (TF), index flexion (IF), middle flexion (MF), ring flexion (RF), little flexion (LF), wrist abduction (WAb), wrist adduction(WAd), wrist flexion(WF), wrist extension(WE), wrist pronation (WP) and wrist supination (WS) (see Figure 4.1C). This sequence was repeated 4 times, so that each movement was performed 4 times for a total of 72 movements. One trial lasts 10 seconds and was followed by 3s of rest (no movement). The patient was asked to mimic with the intact arm the phantom movement in order to control whether each movement was correct.




*4.1* ***High-density sEMG setup and task.*** *A) HDEMG grids position on flexors stump muscles (top) and extensor stump muscles (bottom). B) Representation of HDEMG grids and electrode numbering; red line divides flexors muscles (left) from extensor muscles (right). C) Phantom* *movements performed: open hand (OH), close hand (CH), thumb extension (TE), index extension (IE), middle extension (ME), ring extension (RE), little extension (LE), thumb flexion (TF), index flexion (IF), middle flexion (MF), ring flexion (RF), little flexion (LF), wrist abduction (WAb), wrist adduction (WAd), wrist flexion(WF), wrist extension (WE), wrist pronation (WP) and wrist supination (WS).*

#### *4.2.1.4. High-Density Electromyographic signals recordings and processing*

Surface High-Density electromyographic (HDEMG) signals from flexor and extensor muscles of the stump (Figure 4.1A, B) were acquired by using a semi-disposable adhesive grid of 64 electrodes (GR10MM0808, OT Bioelettronica, Torino, Italy). The grid was made of 8 rows and 8 columns of electrodes (1-mm diameter, 10-mm interelectrode distance in both directions). Muscles areas were identified by asking to the patient to perform wrist extension or wrist flexion, using radius and ulna as reference. The grids were fixed at the subject skin by adhesive tape. The part of the skin where the grid was located was slightly abraded with abrasive paste (Medic-Every, Parma, Italy). Conductive gel was inserted into the cavities of the grid to assure proper electrode skin contact.

HDEMG data were stored applying a band-pass filter between 10 and 500 Hz and sampled at 5120 Hz per channel. Signals from each of 128 channels were rectified and then the root mean squared (RMS) from the first 4 seconds were calculated

#### *4.2.1.5. Pattern recognition algorithm*

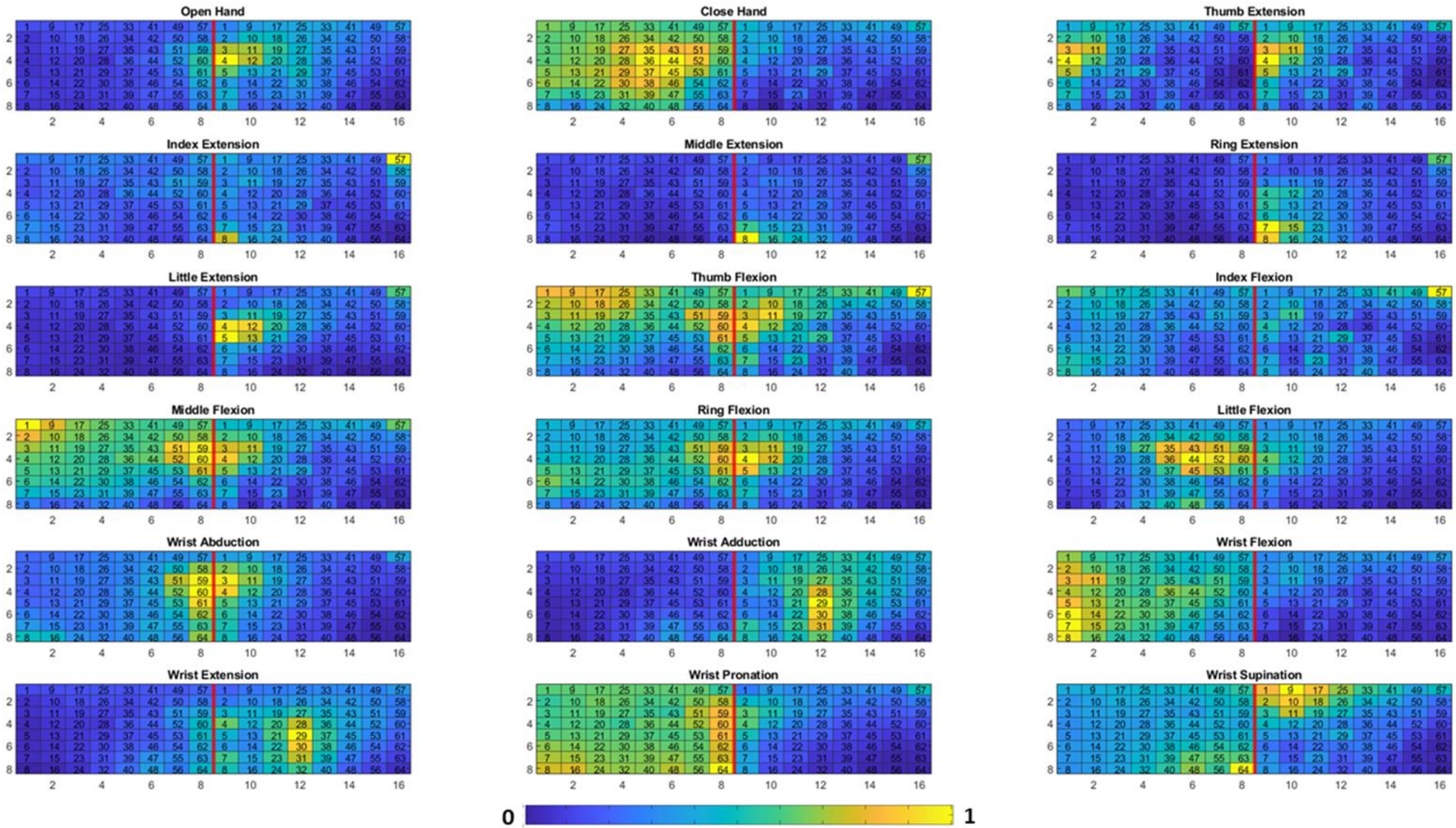
In order to test the possibility to use HDEMG to classify different phantom movements, the 72x128 matrix fed into a Linear Discriminant Analysis (LDA) classifier. Rows represented each single trials and columns the RMS values calculated from 128 HDEMG channels. Features were transformed in z-scores. A leave-one-out cross-validation was applied in order to ensure no overestimation. Finally, the significance of model accuracy was tested by using permutations test (n permutations = 500).

#### *4.2.1.6. Channel selection for dimensionality reduction*

An automated channel selection based on neighborhood component analysis (NCA) was used. This classification supervised learning method with Euclidian distance was implemented as it provides the specific weight of each single features. The first N features with w (i.e. feature weight) higher than 0.1 was selected and these features fed into an LDA as in 4.1.2.5.

### 4.2.2. Results

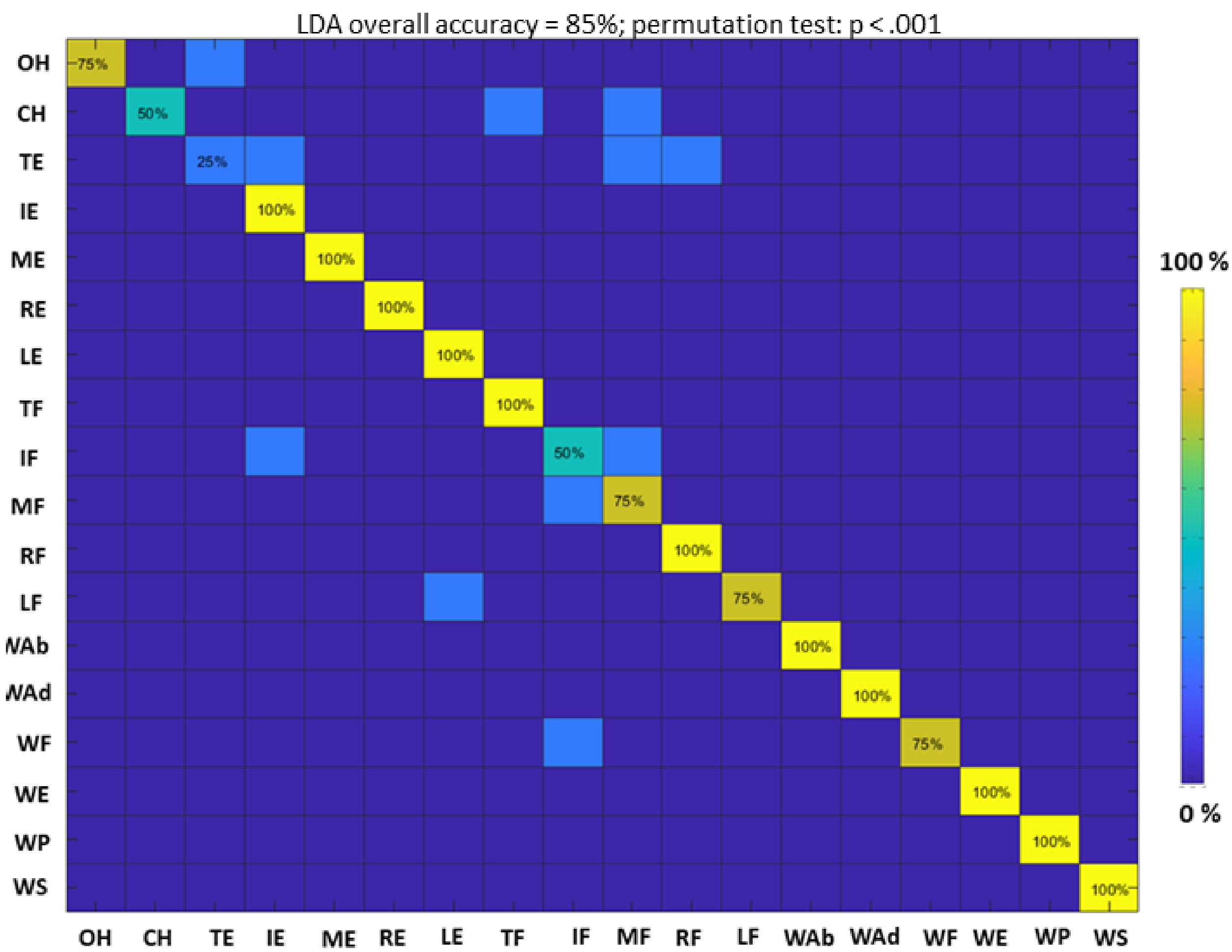
Muscles activity showed a specific spatial pattern for each phantom movement as shown in Figure 4.2.




4.2. **Spatial HDEMG activity during specific phantom movements**. Electrodes number and division between flexors and extensors are represented as in Figure 4.1B. Data for each matrix were normalized within electrodes and between movements. Normalization was calculated between 0 (no activity) and 1 (maximum activity).

#### *4.2.2.1. Classify phantom movements*

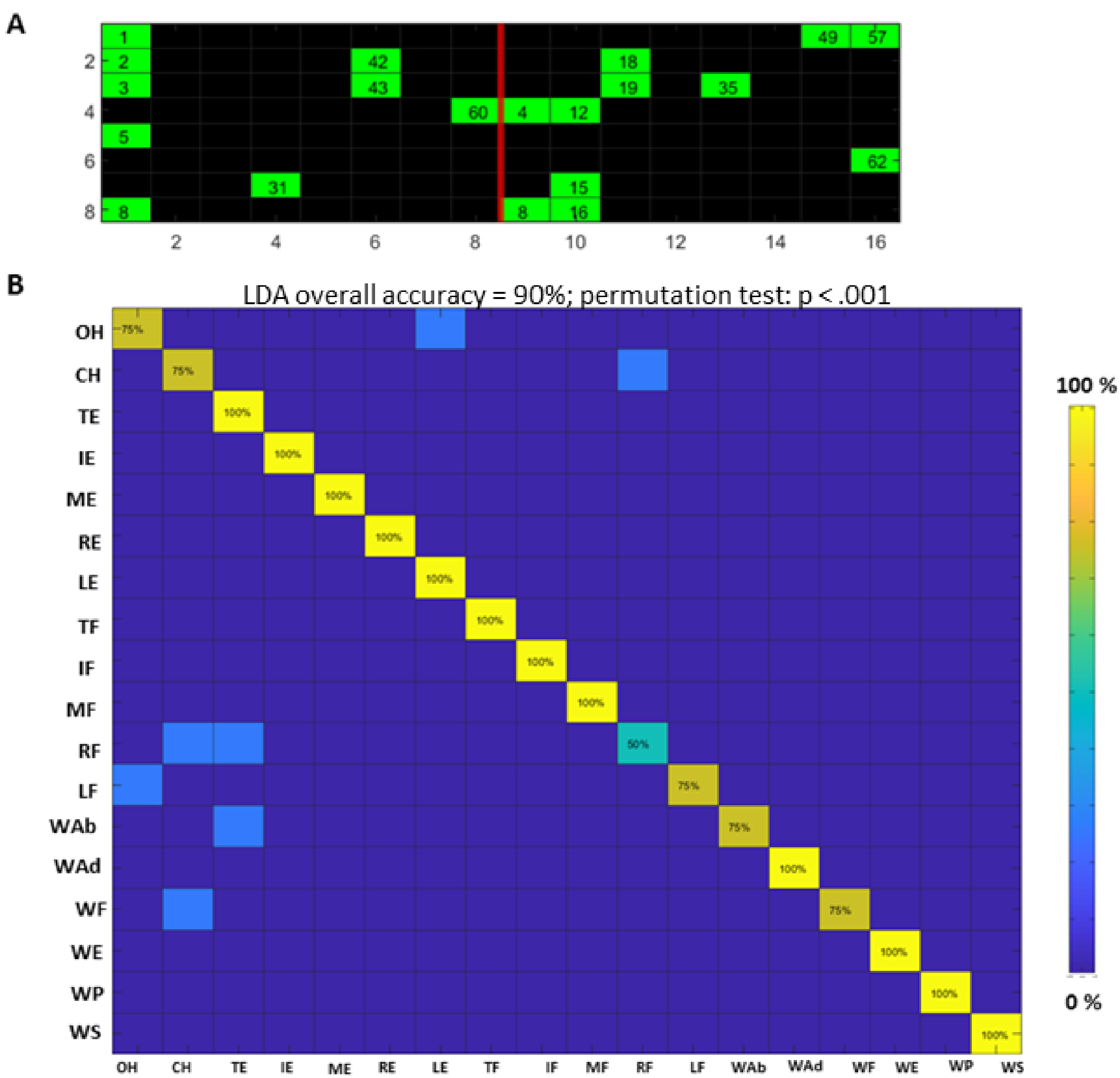
I investigated the possibility to use HDEMG to decode a large number of different phantom movements, i.e. 18. Results from LDA with 128 features (see 4.2.1.5) showed a high classification accuracy, i.e. 85% (Figure 4.3). The pattern recognition algorithm failed to classify thumb extension (25%), close hand (50%) and index flexion (50%). Differently, all the others movements were classified with an accuracy above 75%. Moreover, in order to exclude a possible overestimation due to the high number of features, I performed permutation test showing that the high performance accuracy was not linked to the number of features ($p < .001$).




*4.3.* ***Linear discriminant analysis with 128 features confusion matrix.***

#### *4.2.2.2. Improving classification accuracy by electrodes selection*

By using NCA algorithm the number of features was reduced, i.e. the number of muscular activity sites, from 128 to 20 (Figure 4.4A). LDA applied to selected channels showed an improvement of classification accuracy, i.e. 90% (permutation test: $p < .001$, Figure 4.4B).




*4.4.* ***LDA performed on channel selected by dimensionality reduction algorithm.*** *A) The 20 channels selected from the 128. B) LDA with selected 20 features.*

## 4.3. Study 2: A quantitative analysis of muscles reorganization after upper limb amputation

### 4.3.1. Materials and methods

#### *4.3.1.1. Participants*

Seven individuals with acquired unilateral upper limb amputation (2 females, mean age in years ± standard deviation of the mean (SD) = 45 ± 20, six with absent right hand; Table 4.1) were recruited at the INAIL prosthetic center (Vigorso di Budrio (BO), Italy). All of them were transradial amputees (i.e. amputation below elbow) but one transhumeral (i.e. amputation above elbow). Six healthy controls, right-handed (3 females, mean age in years ± standard deviation of the mean (SD) = 30.7 ± 2.5), were also recruited. All subjects provided written informed consent. The study conformed to the standard of the Declaration of Helsinki and was approved by the ethical committees of Bologna-Imola.

*4.1* ***Patients participating to Study 1 details.*** *Note: TR: transradial amputee; TH: transhumeral amputee.*

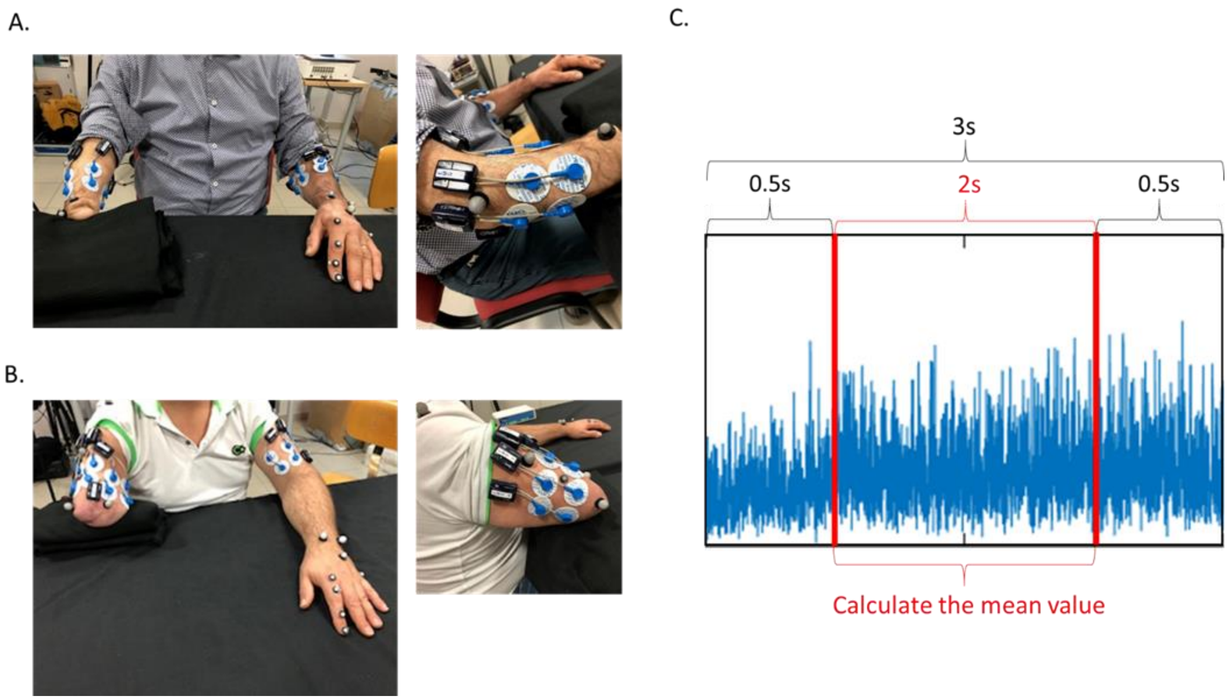
| *Patients* | *Age* | *Sex* | *Time since amputation (years)* | *Cause of amputation* | *Side / dominant* | *Daily prosthesis used* | *Time spent performing phantom movements in a month (%)* | *Difficulty performing single finger flexion* |
|---|---|---|---|---|---|---|---|---|
| *TR001* | 65 | M | 50 | Trauma on work | R / R | Myoelectric | 100 | 0 |
| *TR002* | 22 | M | 1 | Trauma on work | R / R | Kinematic / myoelectric | 60 | // |
| *TR003* | 18 | F | 5 | Trauma on work | R / R | Cosmetic | 20 | 51 |
| *TR004* | 69 | M | 4 | Trauma on work | R /R | Myoelectric | 70 | 74 |
| *TR005* | 39 | F | 15 | Drive accident | L / R | Myoelectric | 100 | 42 |
| *TR006* | 57 | M | 25 | Trauma on work | R / R | Cosmetic / myoelectric | 80 | 19 |
| *TH001* | 45 | M | 5 | Trauma on work | R / R | Myoelectric / Kinematic | 50 | 30 |

#### *4.3.1.2. Phantom movements rating*

All seven patients reported being able to perform phantom movements voluntary. As already found in previous studies (De Graaf et al., 2016), patients reported that phantom movements were often effortful and with small amplitude. Before the experiments, patients were involved in a brief interview in which I explored two aspects of their ability to perform phantom movements. Firstly, I asked them how many times they performed phantom movements during the last month, from 0, that means never, to 100, that means always. Secondly, I asked to rate the difficulty to perform movement of single phantom finger and I calculated the average across fingers to obtain the magnitude of difficulty to perform phantom fingers movements. See Table 4.1 for individual ratings.

#### *4.3.1.3. Electromyographic signals recordings*

Superficial electromyographic (sEMG) signals were acquired by using bipolar wireless electrodes (MiniWave wireless EMG technology, Cometa Systems). In transradial amputees and healthy control subjects 4 sEMG bipolar electrodes were placed on forearm muscles (Figure 4.5A), specifically on wrist flexor carpi ulnaris (WFu), wrist flexor carpi radialis (WFr), wrist extensor carpi ulnaris (WEu) and wrist extensor carpi radialis (WEr). The sEMG areas were detected by palpating the forearm area while I asked to participants to perform combined wrist movements: wrist adduction and wrist flexion to find WFu, wrist abduction and wrist flexion to find WFr, wrist adduction and wrist extension to find WEu and wrist abduction and wrist extension to find WEr. When amputees reported that it was difficult to perform that specific movement with the phantom hand the ulnaris and radialis bones was used to detect the area. In the transhumeral amputee, 2 sEMG bipolar electrodes on biceps and 2 on triceps (Figure 4.5B) were placed. The position of sEMG electrodes was identical between the two arms. Skin area was prepared by using a scrub and conductive cream in order to reduce the skin impedance. All data were sampled at 2 kHz, digitized, and stored for offline analysis using Vicon Nexus software (version 2.9).




*4.5 A) Representation of sEMG position in transradial amputees. B) sEMG position in transhumeral amputee. C) Example of rectified EMG signal of one specific trial and the relative segmentation for the analyses.*

### *4.3.1.4. Electromyographic signals analysis*

Signals from each channel were rectified, the first and last 500 milliseconds were deleted and the signal absolute mean value was calculated from the 2 central seconds (i.e. while patients held the movement (Figure 4.5C). The first part of the signal was removed because movement onset can often be characterized by a burst in EMG amplitude that exceeds the steady-state amplitude associated with the "hold" phase of a movement. Two datasets were considered, the stump/right dataset, based on sEMG placed on stump in amputees and on right arm in HC subject, and the intact/left dataset, based on sEMG on intact arm in amputees and on left arm in HC subject. Each dataset contained participant code, trial type (i.e. movement performed) and the four features based on the four sEMG. Muscle features were transformed in z-score and fed into a Linear Discriminant Analysis (LDA) classifier. Per each participant I created four classification models: (1) stump-stump / right-right, in which the classifier was trained and tested on the stump/right dataset; (2) intact-intact /left-left, in which the classifier was trained and tested on the intact/left dataset; (3) stump-intact / right-left, in which the classifier was trained on the stump/right dataset and tested on the intact/left dataset; (4) intact-stump / left right, in which the classifier was trained on the intact/left dataset and tested on the stump/right dataset. For all models, a leave-one-out cross-validation was applied in order to ensure no overestimation. Finally, the significance of model accuracy was tested by using permutations test (n permutations = 1000).

#### *4.3.1.5. Experiment 1 – Stump muscles reorganization for hand movements*

##### 4.3.1.5.1. Task execution

Both patients and healthy control subjects were seated in a comfortable chair with their intact/left forearm and stump/right forearm placed on a table. Healthy control subjects were asked to perform requested movement with the right wrist/hand and mimic it with the left wrist/hand; while, patients were asked to mimic the movement performed by the phantom wrist/hand with the intact wrist/hand. The wrist/hand movements were: wrist flexion (WF), wrist extension (WE), close hand (CH), open hand (OH) and pinch with three fingers (P3). Thus, intact movements performed by patients and left hand in healthy controls, mimicked the phantom/right movements in order to have the same range of motion and the same speed. Participants after performing a movement held that position for 3 seconds. Rest position without any phantom or intact movements was also recorded. Transradial amputees and healthy control subjects repeated each movement 5 times while the transhumeral amputee repeated each movement 3 times. A total of 30 trials were performed by each transradial amputees and by the healthy control subject (25 hand movements + 5 rest) and 18 by the transhumeral amputee (15 hand movements + 3 rest). Trials order was fully randomized.

4.3.1.5.2. Results and discussion

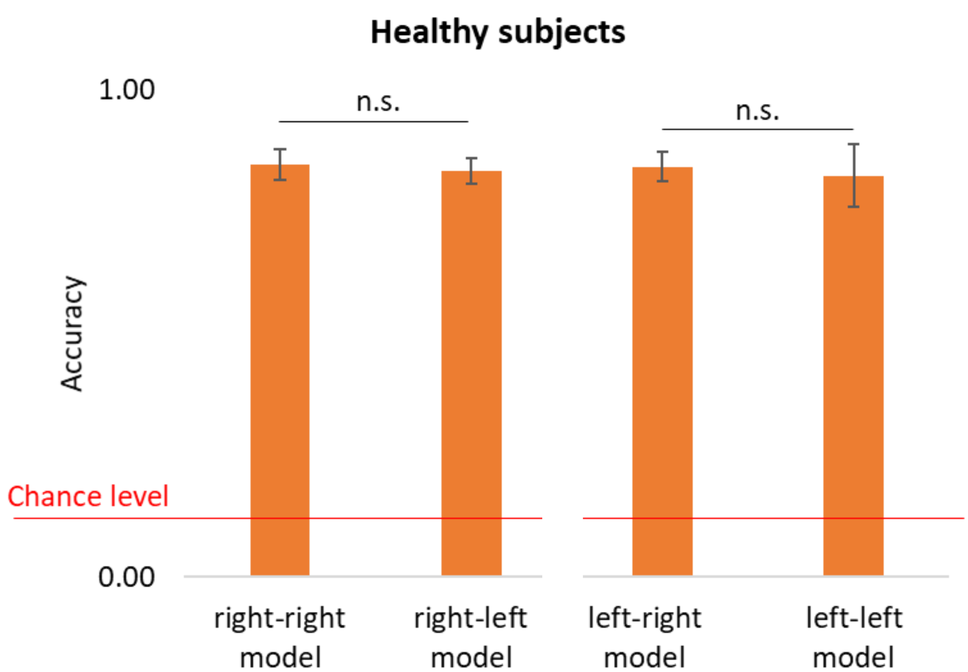
Results from all participants are reported in Table 4.2.

*4.2* ***Single participants results from experiment 1 (i.e. wrist/hand movements).*** *HC: healthy control subject; TR: transradial amputee; TH: transhumeral amputee; HC/TR mean ± SE: mean of accuracies and standard error of the mean calculated considering respectively healthy control or transradial amputees results.*

| *Participants* | *stump-stump model ACC / permutations test significance* | *stump-intact model ACC / permutations test significance* | *intact-stump model ACC / permutations test significance* | *intact-intact model ACC / permutations test significance* |
|---|---|---|---|---|
| *HC001* | 0.86 / p < .001 | 0.83 / p < .001 | 0.81 / p < .001 | 0.61 / p < .001 |
| *HC002* | 0.89 / p < .001 | 0.83 / p < .001 | 0.89 / p < .001 | 0.86 / p < .001 |
| *HC003* | 0.81 / p < .001 | 0.83 / p < .001 | 0.78 / p < .001 | 0.94 / p < .001 |
| *HC004* | 0.94 / p < .001 | 0.92 / p < .001 | 0.97 / p < .001 | 0.97 / p < .001 |
| *HC005* | 0.86 / p < .001 | 0.86 / p < .001 | 0.78 / p < .001 | 0.92 / p < .001 |
| *HC006* | 0.72 / p < .001 | 0.72 / p < .001 | 0.83 / p < .001 | 0.64 / p < .001 |
| *TR001* | 0.83 / p < .001 | 0.50 / p < .001 | 0.67 / p < .001 | 0.77 / p < .001 |
| *TR002* | 0.80 / p < .001 | 0.37 / p < .01 | 0.10 / p > .05 | 0.50 / p < .001 |
| *TR003* | 0.67 / p < .001 | 0.33 / p < .05 | 0.33 / p < .05 | 0.80 / p < .001 |
| *TR004* | 0.87 / p < .001 | 0.43 / p < .001 | 0.27 / p > .05 | 0.63 / p < .001 |
| *TR005* | 0.93 / p < .001 | 0.80 / p < .001 | 0.63 / p < .001 | 0.77 / p < .001 |
| *TR006* | 0.77 / p < .001 | 0.40 / p < .01 | 0.50 / p < .001 | 0.48 / p < .001 |
| *TH001* | 0.39 / p < .05 | 0.06 / p > .05 | 0.22 / p > .05 | 0.17 / p > .05 |
| *HC mean ± SE* | 0.85 ± 0.03 | 0.83 ± 0.03 | 0.84 ± 0.03 | 0.82 ± 0.06 |
| *TR mean ± SE* | 0.81 ± 0.04 | 0.47 ± 0.07 | 0.42 ± 0.09 | 0.66 ± 0.06 |

4.3.1.5.3. Healthy control subject

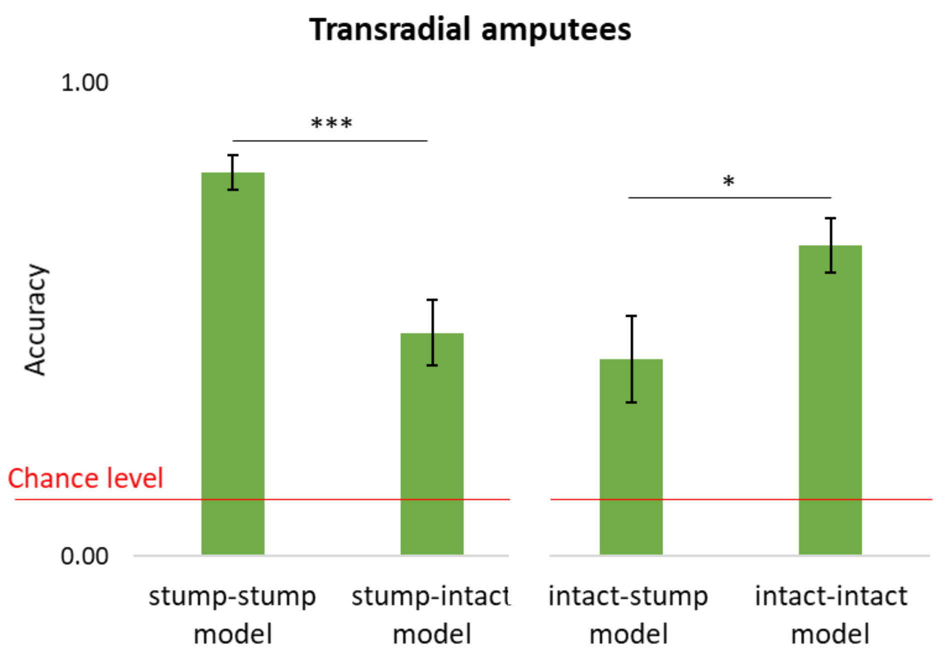
Both right-right and left-left models reached accuracy above 0.80 (mean accuracy across healthy control subjects ± standard error of the mean (SEM), 0.85 ± 0.03 and 0.82 ± 0.06 respectively), showing specific sEMG patterns for specific wrist and hand movements (Table 4.2). When the model was trained on one arm and tested on the other the accuracy was similar (right-left model mean accuracy: 0.83 ± 0.03, left-right models mean accuracy: 0.84 ± 0.03; Table 4.2). It is important to note that the mean accuracies were similar between all the models (Figure 4.6). In particular, right-right model accuracy was not different from right-left model accuracy ($t(5) = 1.31$; $p > .05$), and also left-left model accuracy was not different from right-left model accuracy ($t(5) = -0.40$; $p > .05$). These results showed that flexor and extensor wrist muscles activation was identical between the two arms. Model accuracies were significant as reported by permutations tests.




*4.6* ***Mean models' accuracies from healthy subjects results in experiment 1.*** *Asterisks show paired samples t-test significance. ***: p < .001; *: p < .05; n.s.: p > .05*

#### 4.3.1.5.4. Transradial amputees

Stump-stump model showed high classification accuracy (mean accuracy across transradial amputees ± standard error of the mean (SEM) = 0.81 ± 0.04); permutations test showed that model accuracies were significant for all transradial amputees (see Table 4.2). Each transradial amputee model accuracy was significant (permutations test: $p < 0.001$). Models trained and tested on different arms showed a drop of the accuracies (lower than 0.50, see Table 4.2). In particular, stump-intact model reached 0.47 ± 0.09 and it was significantly lower than stump-stump model (paired samples t-test; $t(5) = 7.34$; $p < .001$, see Figure 4.7); intact-stump model reached 0.42 ± 0.07 and it was significantly lower than intact-intact model (paired samples t-test; $t(5) = -3.04$; $p < .05$, see Figure 4.7). Moreover, I tried to correlate stump-stump model single subject accuracy and the years from the amputation, but there was not any correlation (Pearson's $r = .14$; $p > .05$). Differently, a positive significant correlation between the accuracies and the time patients spent to perform the requested phantom movements during the last six months was found (Pearson's $r = .82$; $p < .05$).




*4.7* ***Mean models' accuracies from transradial amputees results in experiment 1.*** *Asterisks show paired samples t-test significance. ***: p < .001; *: p < .05; n.s.: p > .05*

4.3.1.5.5. Transhumeral amputees

A transhumeral amputee was tested recording sEMG activities from biceps and triceps muscles. Stump-stump model showed that it is possible to discriminate specific patterns related to different phantom movements (ACC = 0.39; chance level = .17, six categories). The permutations test confirmed a specific structure in the data ($p < .01$). Differently, intact-intact model reached .17 accuracy without any structure in the data as shown by a not significant permutations test ($p > .05$). Accuracies from stump-intact and intact-stump model were lower and not significant (ACC = 0.06, $p > .05$; ACC = 0.22, $p > .05$ respectively).

*4.3.1.6. Experiment 2 – Stump muscles reorganization for single finger movements*

All patients were tested in experiments 2 but one (TR002). With experiment 2, it was tested whether the muscles reorganization was related also to fine movements.

4.3.1.6.1. Task execution

The only one difference from the experiment 1 was the performed movements. The phantom movement requested to participants was the flexion of each single fingers. A total of 30 trials were performed by each transradial amputees and by the healthy control subject (25 single finger flexion, 5 per each finger, + 5 rest) and 18 by the transhumeral amputee (15 single finger flexion, 3 per each finger, + 3 rest). Trials order was fully randomized.

4.3.1.6.2. Results

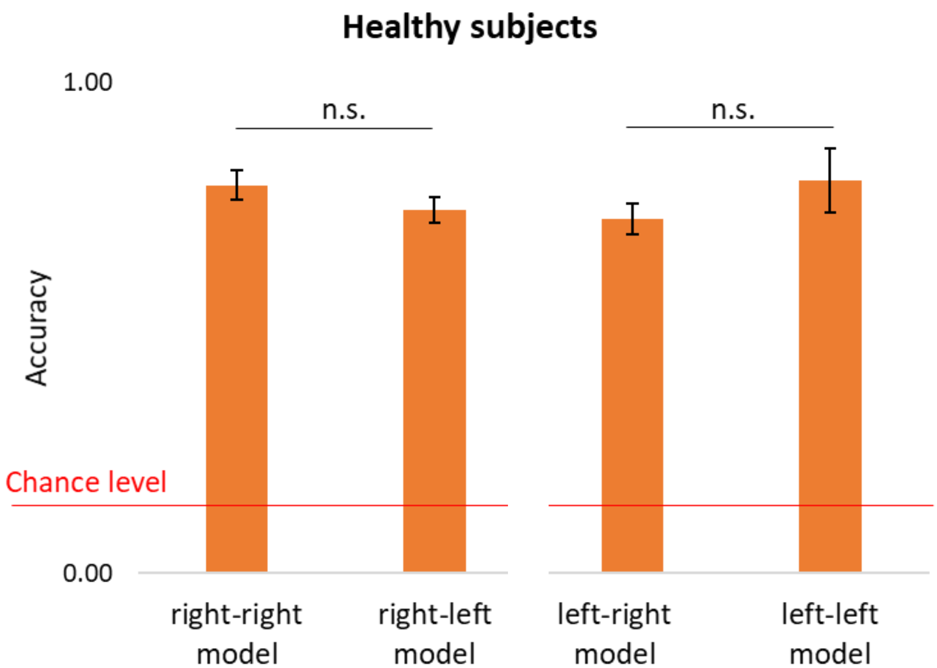
Results from all participants are reported in Table 4.3.

*4.3* ***Single participants results from experiment 2 (i.e. single finger flexion).*** *HC: healthy control subject; TR: transradial amputee; TH: transhumeral amputee; HC/TR mean ± SE: mean of accuracies and standard error of the mean calculated considering respectively healthy control or transradial amputees results.*

| *Participants* | *stump-stump model ACC / permutations test significance* | *stump-intact model ACC / permutations test significance* | *intact-stump model ACC / permutations test significance* | *intact-intact model ACC / permutations test significance* |
|---|---|---|---|---|
| *HC001* | 0.78 / p < .001 | 0.64 / p < .001 | 0.58 / p < .001 | 0.69 / p < .001 |
| *HC002* | 0.75 / p < .001 | 0.61 / p < .001 | 0.61 / p < .001 | 0.78 / p < .001 |
| *HC003* | 0.69 / p < .001 | 0.78 / p < .001 | 0.75 / p < .001 | 0.72 / p < .001 |
| *HC004* | 0.97 / p < .001 | 0.86 / p < .001 | 0.81 / p < .001 | 0.83 / p < .001 |
| *HC005* | 0.86 / p < .001 | 0.78 / p < .001 | 0.81 / p < .001 | 0.81 / p < .001 |
| *HC006* | 0.69 / p < .001 | 0.78 / p < .001 | 0.78 / p < .001 | 0.97 / p < .001 |
| *TR001* | 0.97 / p < .001 | 0.01 / p > .05 | 0.07 / p > .05 | 0.80 / p < .001 |
| *TR003* | 0.53 / p < .001 | 0.30 / p > .05 | 0.23 / p > .05 | 0.33 / p < .05 |
| *TR004* | 0.93 / p < .001 | 0.33 / p < .05 | 0.5 / p < .001 | 0.67 / p < .001 |
| *TR005* | 0.69 / p < .001 | 0.19 / p > .05 | 0.07 / p > .05 | 0.62 / p < .001 |
| *TR006* | 0.80 / p < .001 | 0.17 / p > .05 | 0.30 / p > .05 | 0.47 / p < .001 |
| *TH001* | 0.42 / p < .01 | 0.08 / p > .05 | 0.04 / p > .05 | 0.21 / p > .05 |
| | | | | |
| *HC mean ± SE* | 0.79 ± 0.04 | 0.74 ± 0.04 | 0.72 ± 0.04 | 0.80 ± 0.04 |
| *TR mean ± SE* | 0.78 ± 0.08 | 0.20 ± 0.06 | 0.23 ± 0.08 | 0.58 ± 0.08 |

4.3.1.6.3. Healthy control subject

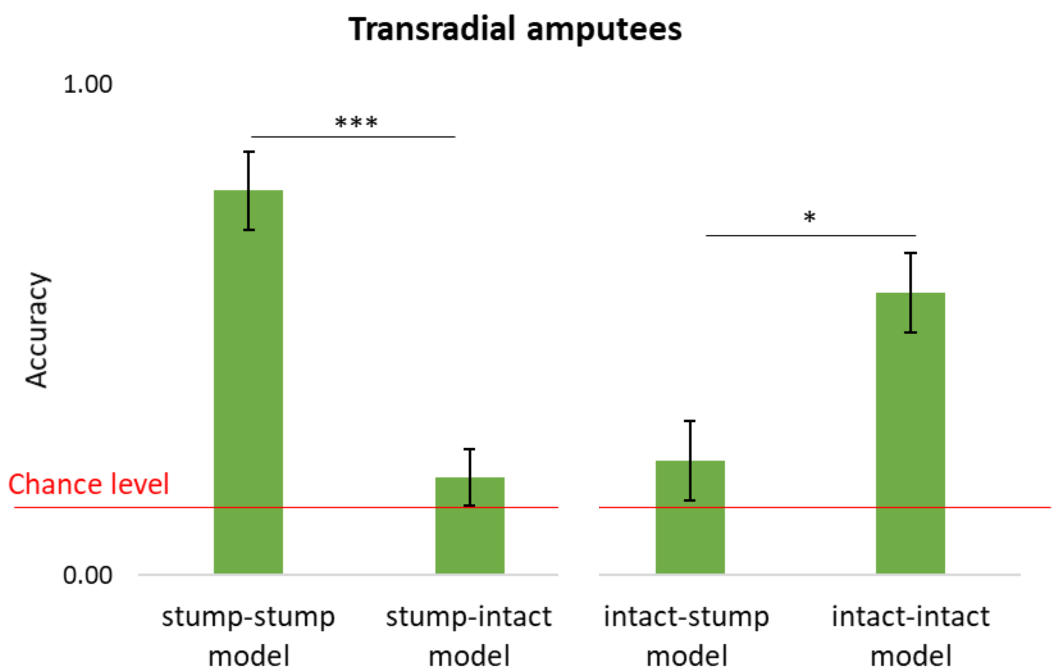
All models performed on healthy control data reached a good classification accuracy and were significant (see Table 4.3). There were not significant differences between accuracies of models trained on one arm and tested on the other as showed by paired sample t-test analyses (right-right model vs. right-left model: $t(5) = 1.08$, $p > .05$; left-right model vs. left-left model: $t(5) = -2.02$, $p > .05$; see Figure 4.8).




*4.8* ***Mean models' accuracies from healthy subjects results in experiment 2.*** *Asterisks show paired samples t-test significance. ***: p < .001; *: p < .05; n.s.: p > .05.*

4.3.1.6.4. Transradial amputees

Stump-stump model highlights that each single patient performed single finger movements by activating specific EMG patterns (mean accuracy across subjects ± SEM = 0.78 ± 0.08); permutations test showed that the accuracies were significant. This result was reported also by intact-intact model (mean accuracy across subjects ± SEM = 0.58 ± 0.08, all accuracies were significant as reported in Table 4.3). Models trained and tested on different arms showed lower accuracies and the permutation tests were not significant for all transradial amputees but one (see Table 4.3). Paired samples t-test showed that models accuracies from stump-intact models were significantly lower than stump-stump models ($t(4) = 4.97$; $p < .001$) and that there were no differences with the intact-stump ones ($t(4) = -.65$; $p > .05$. Figure 4.9). Significant correlation between stump-stump model accuracies and years from amputation was not found (Pearson's r = .55; p > .05). Differently, a negative correlation was found between stump-stump model accuracies and difficulty to perform phantom fingers movements (Pearson's r = -.90; p < .05). This correlation suggests patients are able to recognize their real ability to perform phantom fingers movements, as shown by correlation with their perceived ability.




*4.9* ***Mean models' accuracies from transradial amputees results in experiment 2.*** *Asterisks show paired samples t-test significance. ***: p < .001; *: p < .05; n.s.: p > .05.*

4.3.1.6.5. Transhumeral amputee

In transhumeral amputee stump-stump model reached a significant above chance level accuracy (0.39; permutations test: p < .05), differently, intact-intact model accuracy was not significant (0.17; permutations test: p > .05); moreover, cross-classification reached very low classification accuracy (see Table 4.3).

## 4.4. Study 3: A systematic training protocol for phantom hand movements

### 4.4.1. Methods

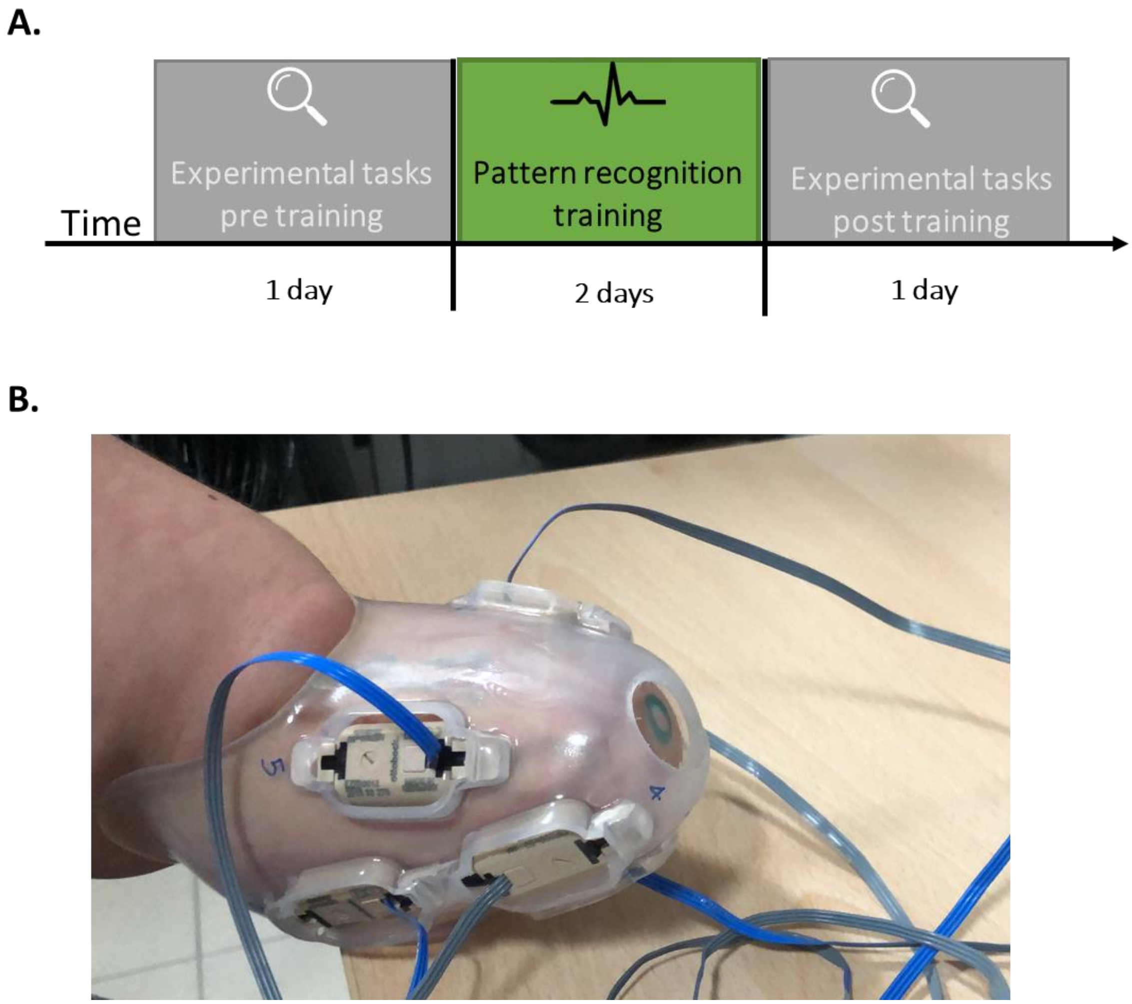
#### *4.4.1.1. Participants*

Participants are the same in structural properties study, see table 3.1. All patients provided written informed consent. The study conformed to the standard of the Declaration of Helsinki and was approved by the ethical committees of Bologna-Imola.

#### *4.4.1.2. Apparatus*

Patients were involved into 4 experimental days. During the first and last day patients performed three different phantom movement tasks, while during the two central days they were involved into the phantom movements training protocol (Figure 4.10A). The phantom movements training was conducted by using EMG Data Acquisition & Training Software (EDATS) developed by INAIL prosthetic center of Vigorso di Budrio (Dellacasa Bellingegni et al., 2017).

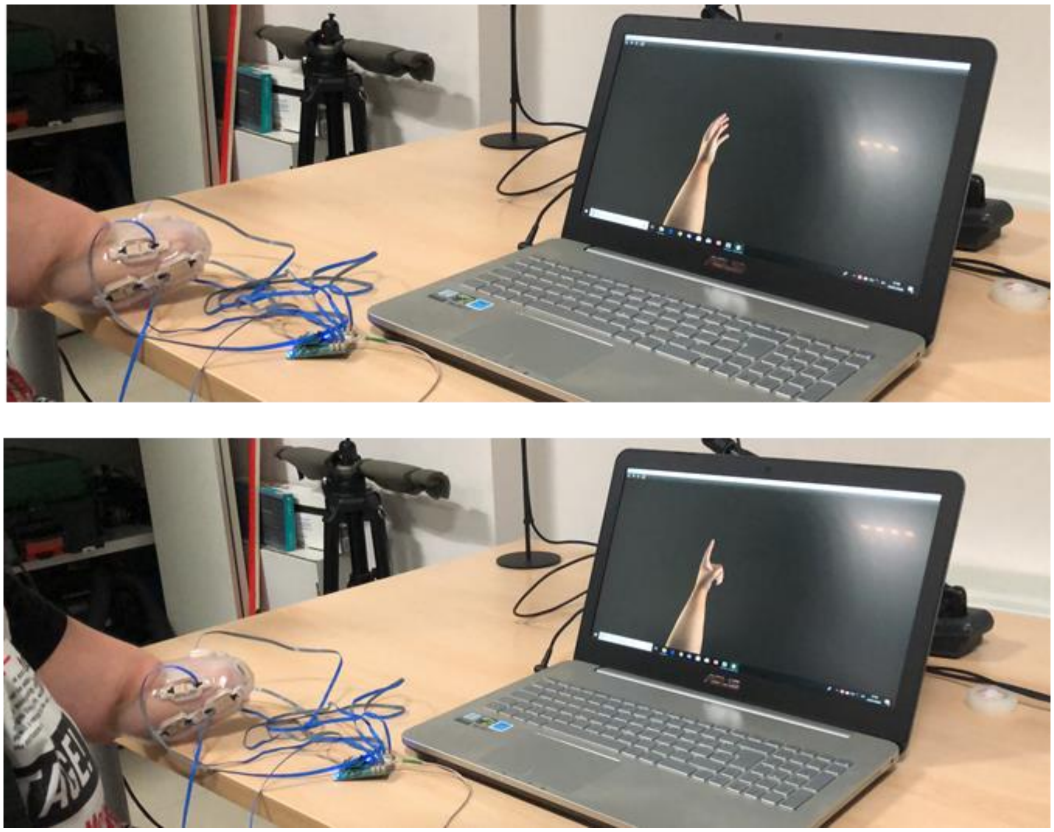
Six sEMG electrodes were placed on the stump, in general close to the followed muscles: wrist flexor carpi radialis, wrist extensor carpi radialis, wrist extensor carpi ulnaris and wrist flexor carpi ulnaris. In order to maintain the electrodes in the same position over the 4 experimental days of experiment, a unique thermoplastic socket was created for each single patient (see figure 4.10B). Before starting, with the physiotherapist, we found the best position for the electrodes for a good muscle activity signal, then the orthotic technician creates the unique socket and placed the six holes for the electrodes.




*4.10 A) Organization of days in Study 3. B) Thermoplastic socket with sEMG that was unique for each patient.*

### *4.4.1.3. Phantom training protocol*

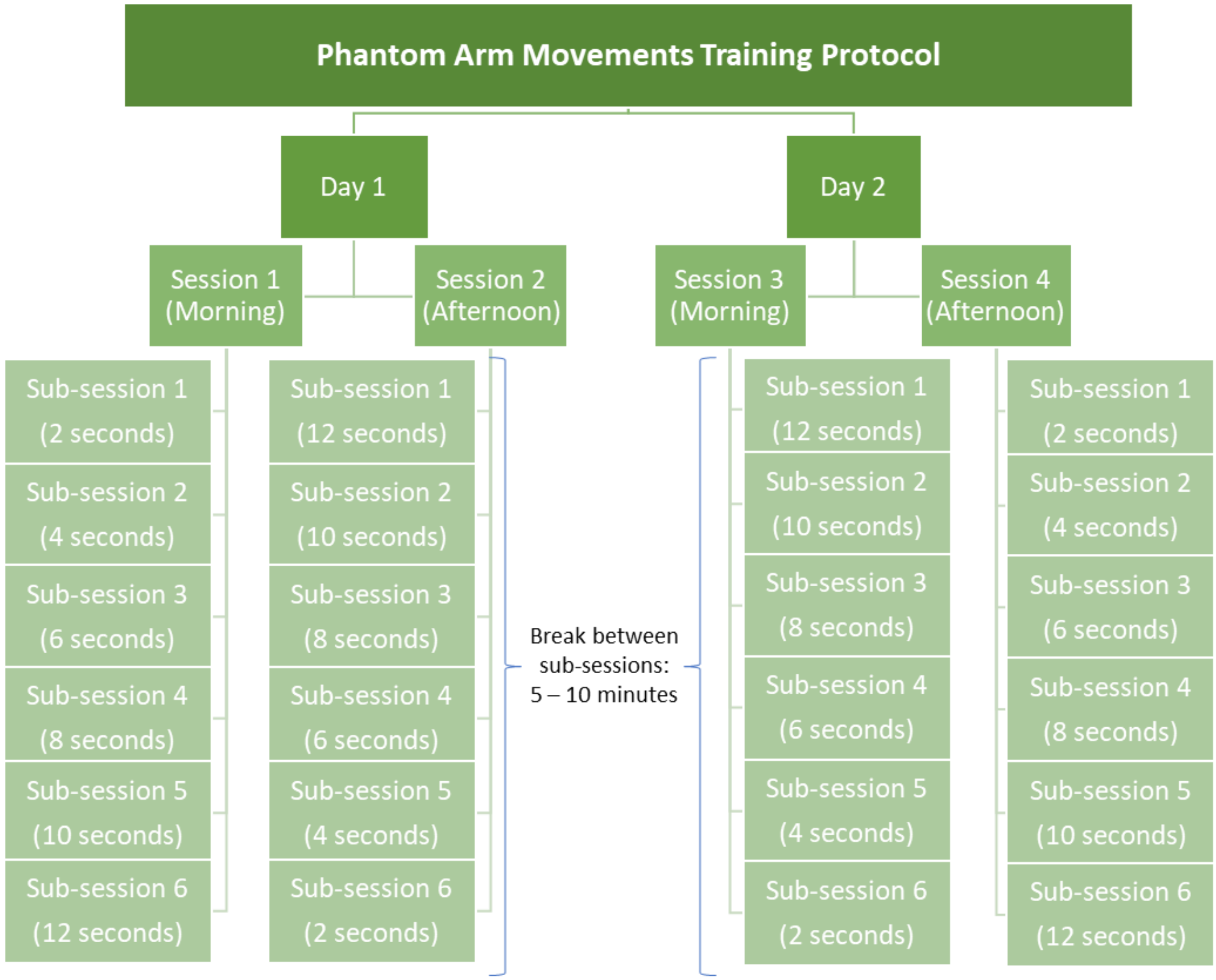
Patients were seated on a comfortable chair in front of a screen of a laptop (15.6 inch) with the stump placed on the table. The EMG electrodes were placed in the custom-made socket. During the training patients performed 4 different phantom movements: hand open, hand close, pinch with three digits and index pointing (Figure 4.13B). The intended movement, as decoded by pattern recognition algorithm implemented in EDATS software, was visualized on the screen of the laptop (Figure 4.11).



*4.11* ***Training of phantom movements with virtual reality.***

In total, patients performed 2 day of training. Each day consisted in two sessions, one in the morning and one in the afternoon.

Each session was divided in 6 sub-sessions in which the time to remain in the specific phantom position could be 12, 10, 8, 6, 4 or 2 seconds. The order of the timing to remain in the specific phantom movements differed between sessions (see figure 4.12).

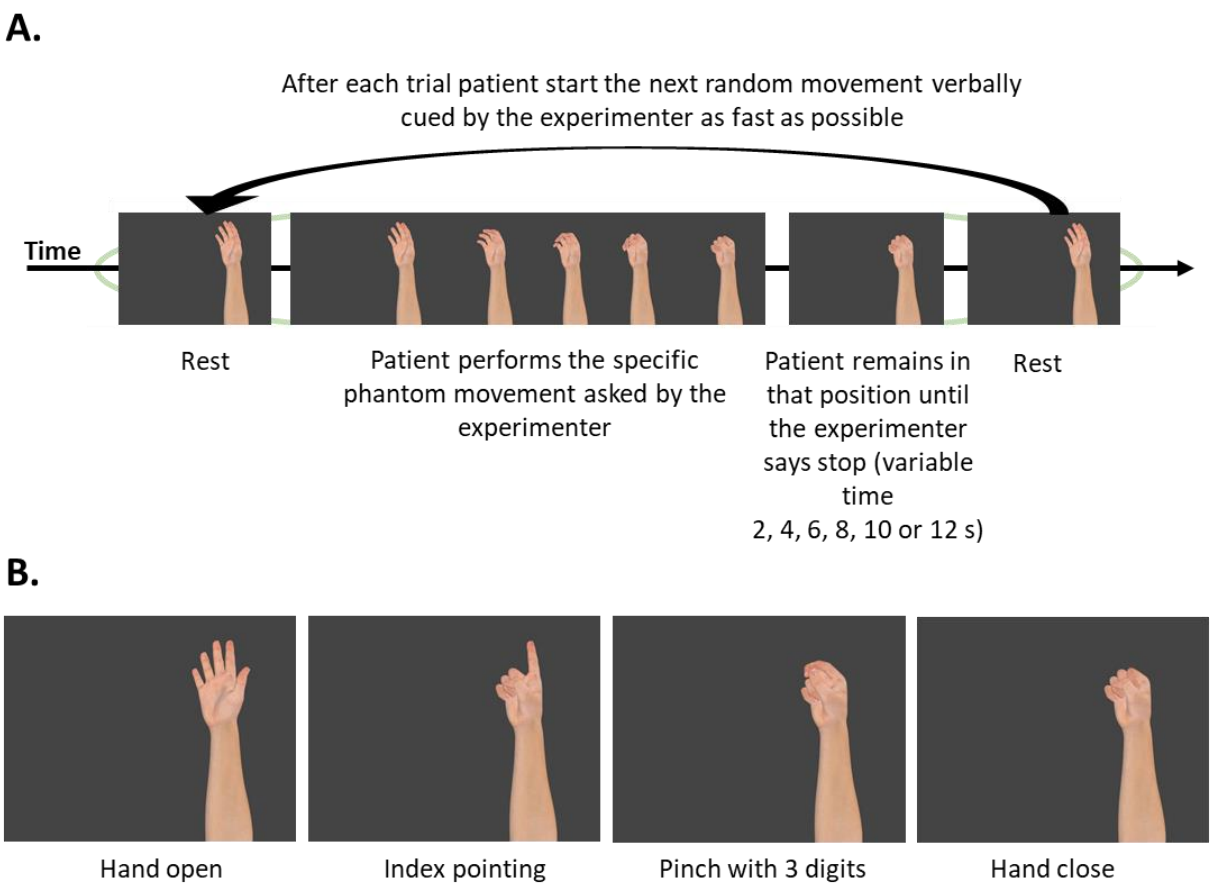



*4.12* ***Schedule of phantom arm movements training protocol.***

Each sub-session was as follows:

- Step 1: training of the algorithm; the algorithm used to classify the four phantom movements plus the rest position was trained asking to the patients to perform 5 times each of the phantom movements and to remain in that position for 3 seconds. The rest position (i.e. no movement) was recorded 4 times. If the algorithm reached a classification accuracy above 95% we passed to step 2, differently we started again with step 1;

- Step 2: the pattern recognition algorithm was used to control a real-time virtual 3D hand shown on the laptop screen;
- Step 3: experimenter verbally cued one specific phantom movement that patients had to perform; once the phantom movements was performed by the virtual hand patients were asked to remain in that position for a specific time. The time was controlled by the experimenter. Patients was instructed to wait in that position until the experimenter said "stop", in that moment he/she could pass to the rest position. Then, the experimenter said the next movement and the patient was instructed to do the movement as fast as possible (Figure 4.13A).




*4.13 A) Schematic representation of single trial in sub-session training. B) Phantom hand movements trained.*

Between each sub-session there was a little break of about 5-10 minutes. In each sub-session patients performed each phantom movement 10 times. The order of the phantom movements to perform was fully randomized using a custom MatLab script.

If during the training patients reported that he/she was actually performing the movement requested but the virtual hand not, the training of the algorithm was repeated as in step 1.

In total in each session patients performed a maximum of 440 phantom movements, 110 per each movement, 10 in each sub-session. If during one session the patient reported that he/she was tired we did a longer break, if after the break he/she was still tired the session was concluded.

#### *4.4.1.4. Experimental tasks procedure*

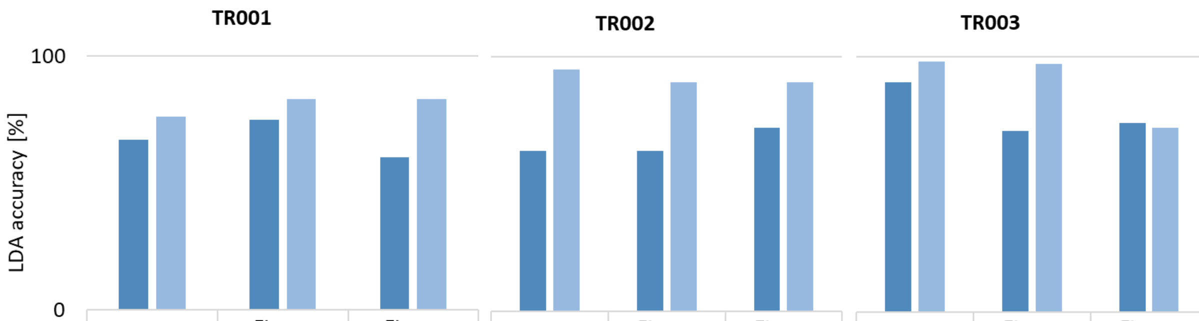
On the day before and the day after the 2-day phantom training protocol, patients performed the experimental tasks in order to evaluate the muscle pattern activity on 15 different phantom movements. Patients were seated on a comfortable chair with the stump place on a table. Each patient started with the phantom hand/wrist movements task in which they performed with the phantom arm, wrist flexion (WF), wrist extension (WE), close hand (CH), open hand (OH) and pinch with three fingers (3P). This was followed by the phantom finger flexion task in which they were instructed to flex each single finger. Finally, they performed the phantom finger extension task in which they were instructed to extend each single finger. Patients after performing the specific requested movement held that position for 3 seconds. In all the tasks the rest condition was added, in which patients were instructed to not move the phantom hand. Phantom hand/wrist movements task consisted in 42 trials (i.e. 7 trials per each movements + 7 trials of rest), while phantom finger flexion and extension tasks consisted in 30 trials (i.e. 5 trials per each fingers + 5 trials of rest). In all the tasks the order of the movements was fully randomized.

#### *4.4.1.5. Data analyses*

Signals from each channel were rectified and the first and last 500 milliseconds were deleted. The 2 central seconds were divided into 10 time bins of 200 ms each. Per each time bin the Root Mean Square (RMS) value was calculated and then it was averaged over the all bins in order to obtain one specific value per each electrode and trial. For each patient three different datasets were created, one per each task. Datasets, containing in rows the trials and in column the muscle features, transformed in z-score, fed into an LDA classifier. A leave-one-out cross-validation was applied in order to ensure no overestimation. Finally, the significance of model accuracy was tested by using permutations test (n permutations = 1000).

#### *4.4.1.6. Results*

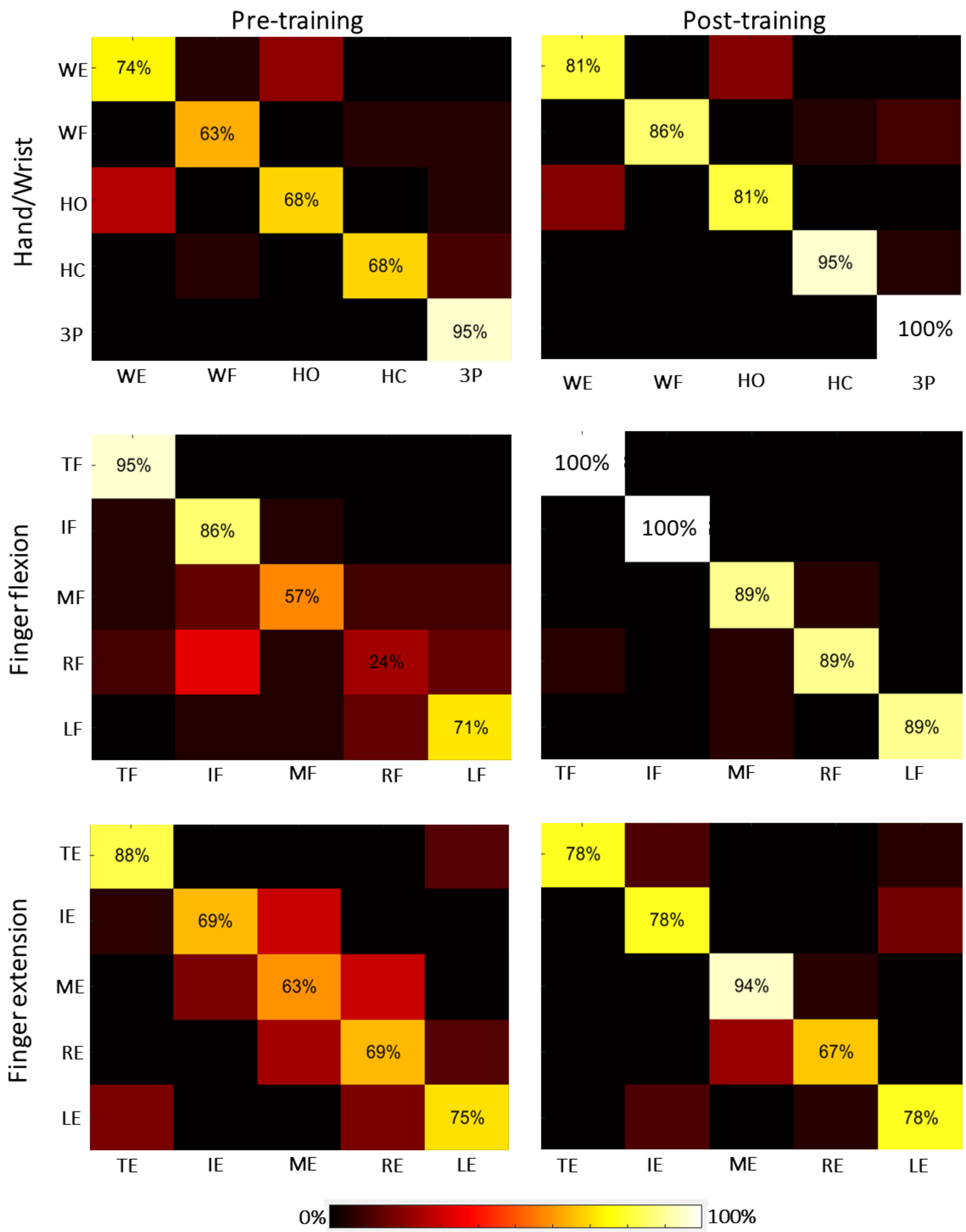
The LDA classifiers showed a better performance after the training for all the patients (Figure 4.14). In particular in TR001 and TR002 model performances were higher in the post-training session than in the pre-training session for all the tasks. Differently, in patient TR003 model performances were higher in the post-training session for the phantom hand/wrist task and phantom finger flexion task, but not for the phantom finger extension task. All model accuracies, tested with permutation test, were significant.




| | Hand/Wrist | Finger Flexion | Finger Extension | Hand/Wrist | Finger Flexion | Finger Extension | Hand/Wrist | Finger Flexion | Finger Extension |
|---|---|---|---|---|---|---|---|---|---|
| Pre | 67 | 75 | 60 | 63 | 63 | 72 | 90 | 71 | 74 |
| Post | 76 | 83 | 83 | 95 | 90 | 90 | 98 | 97 | 72 |

*4.14* ***Models performances pre and post training in each task and subject.***

By averaging the single task confusion matrices across the three patients, it is possible to see that most of the specific phantom movements were better classified after the training (see Figure 4.15).




*4.15* ***Pre and post training single task average of confusion matrices across subjects.*** *Note. Phantom movements performed: wrist extension (WE), wrist flexion (WF), hand open (HO),* *hand close (HC), pinch with three fingers (3P), thumb flexion (TF), index flexion (IF), middle flexion (MF), ring flexion (RF), little flexion (LF), thumb extension (TE), index extension (IE), middle extension (ME), ring extension (RE), little extension (LE).*

## 4.5. General Discussion

All of the results reported in this chapter expand the knowledge about the electromyography properties of phantom arm movements.

In particular, study 1 showed that High Density EMG holds promise as a technique to improve prosthetic control with more than one degree of freedom and highlight that it is possible to use it to decode a high number of different phantom movements. Moreover, this technique could be used to select specific muscles areas for classic surface EMG and pattern recognition algorithm.

The quantitative findings in study 2 are in line with the hypothesis and qualitative observation (Reilly et al., 2006) of a peripheral reorganization after limb amputation. This is supported by the finding of overall lower stump-to-intact (and intact-to-stump) cross-classification accuracies compared to stump-to-stump (and intact-to-intact) accuracies. Moreover, whilst all cross-classification models reached significant above chance-level accuracy in experiment 1 (arm/hand movements), cross-classification was mostly at chance and permutation tests were not significant in experiment 2 (single finger movements). This finding supports the hypothesis that after amputation EMG pattern undergo a reorganization, and that this reorganization is most prominent for phantom movements not directly controlled by that specific muscles. This is further supported by the results from transhumeral amputees. Indeed, results from transhumeral amputee data showed a strong reorganization, also in muscles not directly involved in fingers movements, that could allow transhumeral amputees to perform different phantom movements and use them to control the prosthesis. One implication of these results is that pattern recognition algorithm, developed for prosthetic control, should be trained and tested directly on amputees rather than on healthy subjects (Kristoffersen et al., 2019). As previous studies suggested (Kikkert et al., 2018; Wesselink et al., 2019), these peripheral reorganizations establish the hand representation at central/cortical level. Future studies should investigate the possible reorganization at middle level, i.e. at the spinal cord level. Moreover, it is possible to speculate that this peripheral reorganization is directly related to the ability (and maybe the self-training) to perform these movements and not to the time from the amputation. Thus, the reorganization could be not spontaneous but induced by trainings. Indeed, found correlation in experiment 1 demonstrates the importance to train stump muscles with phantom wrist/hand movements to improve the possibility to use polyarticulated prostheses. Moreover, this correlation highlights the importance to develop a specific training for phantom hand/wrist movements. Often, phantom sensations are thought only as phantom limb pain, and many amputees, afraid by this pain, do not even try to perform phantom movements. Despite this, recent studies suggest that phantom motor execution decrease phantom limb pain (Ortiz-Catalan, 2018; Ortiz-Catalan et al., 2016; Raffin et al., 2016), adding evidence to the importance of phantom movements training.

In study 3, I proposed a 2-day phantom arm movement training protocol. Only few previous studies investigated about the functional effects of training phantom movements. Moreover, no specific phantom movement training protocol is currently standardized. Powell and Thakor (2013) showed that after 10-days training protocol different phantom movements were easier to discriminate between each other. The 2-day protocol presented here seems to be effective to train and make more distinguishable phantom movements in order to improve patients' abilities to perform different phantom arm movements. Interestingly, while the protocol trained only 4 phantom movements (i.e. hand open, hand close, pinch with three digits and index pointing), the effect of the training was effective for all of the 15 phantom wrist/hand movements tested during the three different tasks. Future studies should explore this phantom training protocol with an increased sample size. Furthermore, it will be interesting to see whether the effect of this training protocol will be stable over time.

Taken together, these three studies highlight the importance of studying phantom movements and exploring their properties to improve the knowledge useful for application in prosthetic control. In this regard, the results of all three studies are highly consistent. The possibility to train phantom movements is strictly related to the reorganization that occurs in residual muscles after limb amputation, and the knowledge of this reorganization is key develop EMG interface for prosthetic control.

*"Curiously, if the object is then pulled away by the experimenter, F.A. (the amputee) often experiences pain because the object is 'being wrenched away from the fingers' ".*

*Franz & Ramachandran, 1998*

# 5. Chapter 5. The kinematic properties of phantom arm

## 5.1. Introduction

While phantom movements cannot be tracked directly, they can be measured indirectly taking of interlimb coordination effects. In a seminal study, Franz and Ramachandran (1998) adopted this approach to investigate spatial coupling effects. This study documented a spatial assimilation effect, whereby drawing circles with the phantom limb while concurrently drawing lines with the intact limb resulted in spatial assimilation between the two shapes. However, because participants were free to move their stump, this could simply reflect assimilation between the stump and the intact limb. To overcome this limitation, I designed a strong, quantitative test of pure of phantom-related coupling effects by tracking the intact limb (tip of index finger) and the stump and simultaneously recording phantom-related EMG. This approach allowed us to directly measure phantom movements (through EMG) while concurrently controlling for any residual contribution of stump movements.

## 5.2. Methods

### 5.2.1. Participants

Seven individuals with acquired unilateral upper limb amputation (2 females; mean age in years ± standard deviation of the mean (SD) = 47.5 ± 7.3; six with absent right hand; Table 5.1) were recruited at the INAIL prosthetic center (Vigorso di Budrio (BO), Italy). All of them were transradial amputees but one transhumeral and can perform phantom arm movements. One right transradial amputee with no phantom arm movement sensation was recruited (age 45). Moreover, four right-handed healthy control subjects (1 female, mean age in years ± standard deviation of the mean (SD) = 27.3 ± 7.6) were also recruited. All participants provided written informed consent. The study conformed to the standard of the Declaration of Helsinki and was approved by the ethical committees of Bologna-Imola.

*5.1* ***Patients participating to kinematic properties study details.*** *Note: TR: transradial amputee; TH: transhumeral amputee; NM: transradial amputee without phantom movement sensations.*

| *Patients* | *Age* | *Sex* | *Time since amputation (years)* | *Cause of amputation* | *Side / dominant* | *Daily prosthesis used* |
|---|---|---|---|---|---|---|
| *TR001* | 64 | M | 49 | Trauma on work | R / R | Myoelectric |
| *TR002* | 31 | M | 8 | Drive accident | R / R | Myoelectric / Kinematic |
| *TR003* | 26 | F | 2 | Trauma on work | R / R | Cosmetic |
| *TR004* | 69 | M | 1 | Trauma on work | L /R | Myoelectric |
| *TR005* | 39 | F | 15 | Drive accident | L / R | Cosmetic |
| *TR006* | 56 | M | 25 | Trauma on work | R / R | Cosmetic / myoelectric |
| *TH001* | 45 | M | 5 | Trauma on work | R / R | Myoelectric / Kinematic |
| *NM001* | 45 | M | 31 | Trauma on work | R / R | Cosmetic / myoelectric |

### 5.2.2. Apparatus

Kinematic data were recorded by using Vicon motion capture system with six infrared cameras (sample rate 100 Hz). Retro-reflective markers were placed on the intact hand (left hand for the heathy control subjects) and on the stump. For the analyses, the marker placed on the tip of the intact (left for the healthy control group) index finger (for both patients and healthy control group) and on the tip of the stump close to the radius bone (only for the patient's group) were used. Electromyographic data were recorded by using two wireless sEMG bipolar electrodes (MiniWave wireless EMG technology, Cometa Systems) placed on the stump. Specifically, electrodes were on wrist flexor and wrist extensor muscles. Electromyographic data were sampled at 2 kHz.

### 5.2.3. Procedure

Participants were seated on a comfortable chair with the elbow of the intact and stump arm on a table. The spatial coupling paradigm (Franz and Ramachandran, 1998; Franz et al., 1991) was used; previous findings using this paradigm showed that, under normal movement conditions, asking a subject to draw circles with one hand while concurrently drawing lines with the other hand results in deviations from the target paths, differently, drawing lines with both hands does not impose any coupling interference. Participants were instructed to perform continuous wrist movements with both hands; with the intact/left hand they draw always a line, differently with the phantom/right hand in the congruent condition (the line and line condition) they draw a line, while in the incongruent condition a circle (the circle and line condition). Healthy control subjects performed the movements continuously for 12 seconds, while patients for 30 seconds. This was due to the fact that phantom movements are slower than intact ones (as reported in De Graaf et al. (2016)) and in order to obtain more cycles of movement. To patient NM001 was asked to try to perform the movement with the phantom hand as he could. In total all participants performed 10 trials, 5 congruent and 5 incongruent. Finally, patients were asked to do not move the stump during the task.

### 5.2.4. Data analysis

Each trial was segmented into each specific cycle by using the intact index finger trajectory. For each cycle the ovalization from the line path was calculated. To do this, an ellipse ("fit_ellipse" MatLab free toolbox) was fitted on each cycle; then, on each fitted ellipse, calculated the *k index* *(4)* was calculated as:

$$k\ index = \frac{b^2}{(a^2 + b^2)} \quad (4)$$

where *b* and *a* represent respectively the short and long axes of the fitted ellipse. Values equal to 0 were related with a line path, equal to 1 with a circle path and between 0 and 1 with an ellipse path.

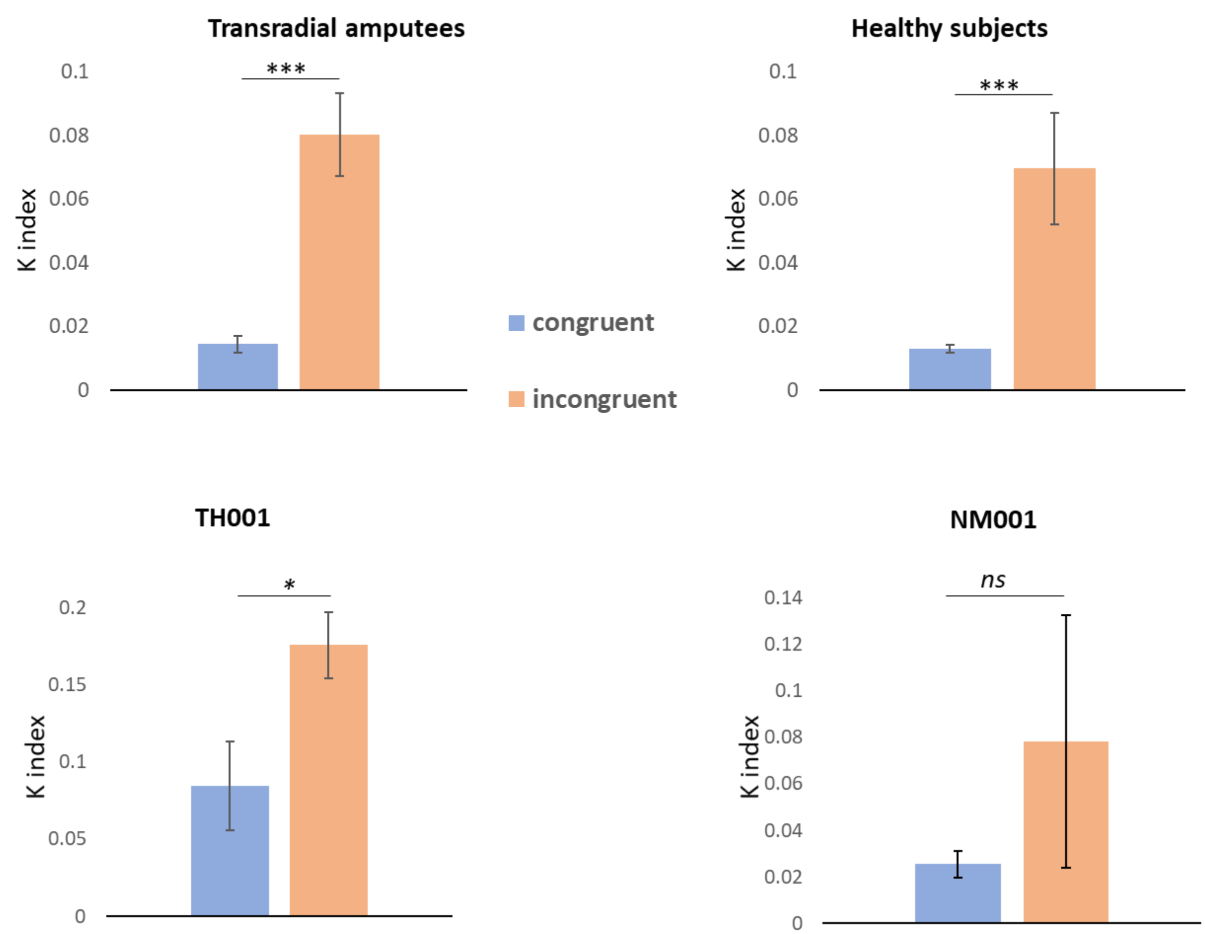
In order to control the stump movement, the *k index* basing on the marker placed on the stump was also calculated. Linear Mixed Effects model was used to statistically test whether, at a single cycle level, k index values differed between congruent and incongruent conditions.

Electromyographic data were rectified and, for each trial, divided into single cycle by using the kinematic of the intact index finger. Per each cycle the mean absolute value was calculated. Single cycle electromyographic data fed into an LDA classifier with 2 features (one per electrodes). A leave-one-out cross-validation was applied and the significance of model accuracy was tested by using permutations test (n permutations = 500).

### 5.2.5. Results

#### *5.2.5.1. Coupling effect in healthy controls and amputees*

The *k index values* were higher for the incongruent condition than for the congruent condition healthy controls (mean difference (i.e. incongruent – congruent) = 0.06, $p < .001$). The same pattern was present in transradial amputees (mean difference = 0.07, $p < .001$) and in transhumeral amputee (mean difference = 0.08, $p < .05$). In contrast, the transradial amputee with no experience of phantom movements showed no spatial coupling effect (mean difference = 0.05, $p > .05$, Figure 5.1).



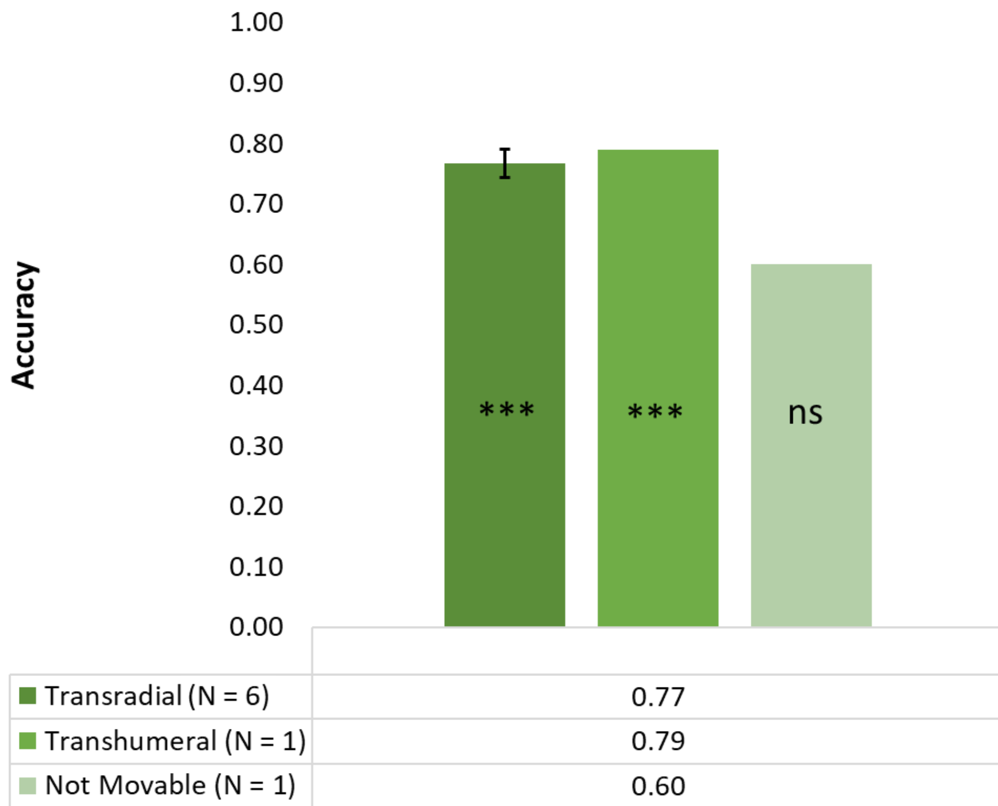

*5.1* ***Spatial coupling effect results****. Note: ns: not significant; *: p < .05; ***: p< .001.*

### *5.2.5.2. Moving the stump or the phantom hand?*

Could spatial coupling effects observed in amputees with movable phantom be due to subtle movements of the stump? To rule out this possibility, a linear regression analysis between the *k index* of intact limb movements and the *k index* of stump movements in amputees with moveable phantom was performed. Results showed no relationship between *k index* values calculated on the index finger and *k index* values calculated on stump in both transradial amputees ($R^2$ = -0.002, p > .05) and in the transhumeral amputee ($R^2$ = 0.011, p > .05).

### *5.2.5.3. Electromyographic activity of spatial coupling task*

To ensure that the patients performed two different movements with phantom hand, the sEMG data were recorded from stump muscles during the task. One single LDA model per each patient was performed. Model accuracies of transradial amputees were averaged across them. Results showed that it was possible to classify the two different movements performed by the phantom hand above chance level (0.5) for both transradial amputees (mean accuracy across patients = 0.77) and transhumeral amputee (accuracy = 0.79). Moreover, permutation test results showed that all models were significant. This result, with the kinematic interference result, demonstrated that patients were performing two different movements. LDA performed on transradial amputee with not movable phantom showed an accuracy above chance (0.60) but the permutation test showed that this was not significant (p > .05, Figure 5.2).




*5.2* ***Accuracy of LDA classifiers****. Note: ns: not significant; ***: p< .001.*

## 5.3. Discussion

Results showed that phantom movements imposed behavioral constraints on intact movements comparable to those evident in control participants moving their intact limbs. This effect was present in transradial amputees with movable phantom sensations but not in the one without movable phantom sensations, replicating and confirming results from Franz and Ramachandran (1998). Coupling interference was also found in the transhumeral amputee. Moreover, results of the present study showed that there were no significant differences in stump movements between the congruent and incongruent conditions; this finding suggest that the interference was related to the specific phantom movement. Finally, results from the LDA classifier showed that both transradial and transhumeral amputees were performing specific phantom movements in relation with the specific condition (i.e. perform lines or circles). Next studies should explore whether coupling effect in amputees with movable phantom is related to the same neural mechanism showed in able bodied subjects during bimanual tasks.

*‘‘Phantoms are a mystery only if we assume that the body sends sensory messages to a passively receiving brain. Phantoms become comprehensible once we recognise that the brain generates the experience of the body. Sensory inputs merely modulate that experience; they do not directly cause it’’*

*Melzack, 1992*

# 6. Chapter 6: Summary

The primary aim of this thesis was to develop a new quantitative framework to investigate phantom arm movements. By combining motion tracking and EMG recording with classification approaches, I found strong support for the hypothesis that phantom arm movements are not phantoms: they are real movements of a dematerialized hand/arm that has the same structure as a real arm/hand. Below, I briefly summarize each chapter before discussing the theoretical and clinical implications of the findings.

Movements can be described and understood at different levels: the cortical level, the muscle level, and the kinematic levels. The findings reviewed in *Chapter 2* suggest that each of these levels, phantom arm movements reflect the operation of the same mechanisms that govern the execution of intact arm movements. This suggests that phantom arm movements are best conceptualized as real movements of a dematerialized arm.

Previous findings reported that patients can perceive the position and shape of their phantom arm. Qualitatively, I report in *Chapter 1* the subjective experience of patient H.K. that said how phantom hand was itching and he/she tried with a voluntary gesture to scratch it not on the stump, but at the level of the prosthetic hand. The results of the study reported in *Chapter 3* show, quantitatively, how the phantom arm can be embodied and how much it can have a specific structure as the intact one. This specific structure is not only present passively but also actively when phantom movement is performed. During reach-to-tap phantom movement the phantom hand structure seemed to remain constant although in one patient with phantom hand inside the stump: in this case the phantom hand displaced outside the stump during movement. This result could be due to a spatial reorganization of the representation of the phantom hand. Future studies, with a lager sample size, should investigate whether in patient with phantom hand inside the stump this position can change during phantom movements.

In *Chapter 4*, I explored the electromyographic properties of the phantom arm movements. As suggested by previous studies, during phantom arm movements the residual stump muscles generate specific pattern of electrical activity. In study 1 I explored the spatial topography of muscles activity during 18 different phantom movements with high-density sEMG. Results showed that each specific phantom movement was related to activity of specific topographic area of the wrist flexor and extensor muscles. Moreover, using high-density patch of electrodes and pattern recognition algorithm, it was possible to discriminate between several different phantom movements. Furthermore, results showed that this approach can be useful to detect the best position for classic bipolar electrodes used for prosthesis control. Indeed, channels selection allowed to improve pattern recognition classification accuracy. Qualitatively, previous findings suggested that these muscles patterns were different from those activated during intact arm movements. Study 2 showed, with quantitative methods, that phantom patterns were different from the patterns activated on the intact arm muscles. This could be related to the fact that after limb amputation a peripheral reorganization occurs, but, as shown by the results, this peripheral reorganization is related to time spent by patients to perform phantom movements, rather than to the time from the amputation. Patient T.S (see 1.2) reported that he tried to train phantom hand movements, and after this, he was able to perceive the movement of each single finger of the phantom hand. Despite this, it is not present a specific training protocol that patients can follow to improve their ability to perform phantom movements. For this reason, it could be useful to develop one training protocol in order to improve the distinguishability between muscles pattern activity during many different phantom arm movements. These patterns can be then used to control new prostheses with more than 1 degree of freedom. Relatedly, in Study 3 I presented a specific phantom arm movements training protocol that resulted to be effective in improving muscle pattern distinguishability. This protocol consisted in 2-days training where patients performed specific phantom arm movements observing them on a virtual hand. Results showed that the distinguishability between phantom movements was higher after the training not only for the phantom movements trained but also for all the phantom arm and hand movements performed by the patients during the post-training tasks.

Another topic I addressed was the kinematic of phantom movements. Patient C.I. reported he/she gesticulate with phantom hand, for instance while talking with others. The kinematic of phantom hand is not possible to track directly, but as seen in *Chapter 2*, many studies analyzed it by tracking it indirectly. Study presented in *Chapter 5*, confirmed previous findings showing that, during bimanual tasks, phantom arm movements imposed behavioral constraints similar to those imposed by movement performed by intact arms. Results on this study added that this constraint was not related to stump movement and that when muscles activity was not related to specific movements the bimanual interference effect was not present.

Collectively, the studies outlined in this thesis demonstrated that what is qualitative perceived by patients, about their phantom arm, is quantitatively evident. Moreover, these results have practical implications in the development of prostheses. From a theoretical perspective, these findings suggest that phantom arm sensation is not an illusory sensation, but have specific structural, muscular and kinematic characteristics, and for this reason can be conceptualized as a real dematerialized arm. The proposed approaches to investigate phantom arm sensation in all its characteristics will help future research to find specific way to implement it in post-amputation patient’s rehabilitation. The present work establishes a first step towards this goal.

## 6.1. Clinical considerations and outlook

From a clinical perspective this work may be important for developing new methods that afford more intuitive control over the multiple degrees of freedom of multi-articulate prosthetic hands.

Next studies could explore how phantom limb structure can co-exist with the prosthesis, and whether this phantom arm can modify, and maybe facilitate, the embodiment of the prosthesis. As patient P.Q. reported (see 1.2), the phantom arm can fill the prosthesis. Thus, it could be interesting to deeply analyze the patients' perception of the phantom hand in order to make the prosthesis more embodied.

Moreover, since patients perceived phantom arm differently and have different ability to control it, in a clinical surgery perspective it could be investigated how amputation techniques impact on these sensations.

Finally, an important goal for future research is to determine the exact sequence of operations across kinematic, muscle, and cortical levels that lead to the generation of phantom movements.

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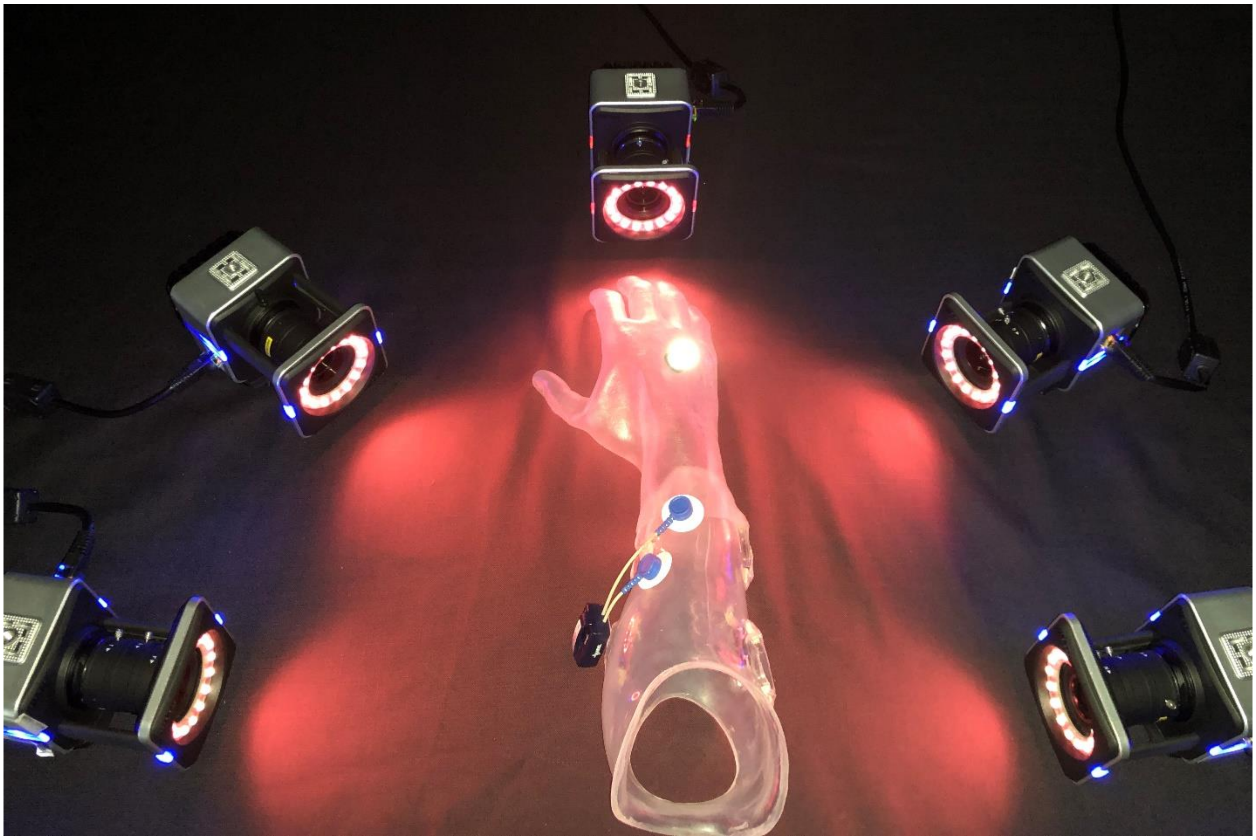

*The prosthesis is the fil rouge that connect technological implementation to life. However, it will always be a simple tool if it does not integrate with the body; phantom limb can ease this with its movement and feeling characteristics.*