amU
Aix Marseille Université

NNT : 2024AIXM0001

THÈSE DE DOCTORAT

Soutenue à Aix-Marseille Université
le 18 décembre 2024 par

Manon CHATEAUX

The sensorimotor loop underlying phantom hand movements in upper limb amputees

Discipline
Sciences du Mouvement Humain

École doctorale
ED 463 SCIENCES DU MOUVEMENT HUMAIN

Laboratoire
Institut des Sciences du Mouvement Etienne-Jules Marey

Composition du jury

Anne KAVOUNOUDIAS Professeure en neuro-sciences à Aix-Marseille Université, Marseille	Examinatrice - Présidente
Yannick AOUSTIN Professeur à l'Université de Nantes	Rapporteur
Thomas LAPOLE Maître de conférence à l'Université Jean Monnet, Saint-Etienne	Rapporteur
Jozina DE GRAAF Professeure à Aix-Marseille Université, Marseille	Directrice de thèse

INSTITUT DES SCIENCES DU MOUVEMENT ETIENNE JULES MAREY

Affidavit

I, undersigned, Manon Chateaux, hereby declare that the work presented in this manuscript is my own work, carried out under the scientific supervision of Jozina De Graaf, in accordance with the principles of honesty, integrity and responsibility inherent to the research mission. The research work and the writing of this manuscript have been carried out in compliance with both the french national charter for Research Integrity and the Aix-Marseille University charter on the fight against plagiarism.

This work has not been submitted previously either in this country or in another country in the same or in a similar version to any other examination body.

Dinan, October the 7th, 2024



This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International Public License

Publications

1. Rossel, O., Chateaux, M., Jarrassé, N., Vérité, F., Touillet, A., Nicol, C., Paysant, J., De Graaf, J.B., 2023. Phantom Movement Training Without Classifier Performance Feedback Improves Mobilization Ability While Maintaining EMG Pattern Classification. IEEE Trans. Med. Robot. Bionics 5, 133–142. https://doi.org/10.1109/TMRB.2023.3237918
2. Chateaux, M., Rossel, O., Vérité, F., Nicol, C., Touillet, A., Paysant, J., Jarrassé, N., De Graaf, J.B., 2024. New insights into muscle activity associated with phantom hand movements in transhumeral amputees. Front. Hum. Neurosci. 18, 1443833. https://doi.org/10.3389/fnhum.2024.1443833

Résumé et mots clés

Cette thèse examine les mécanismes neurophysiologiques des mouvements de la main fantôme chez les amputés du membre supérieur, en se concentrant sur leur lenteur et leur difficulté d'exécution. Elle explore les conséquences de la réorganisation de la boucle sensorimotrice après l'amputation et après un entraînement quotidien à domicile. La mobilité fantôme, qui permet aux amputés de déplacer volontairement leur membre fantôme, illustre la plasticité du système nerveux adulte. Le premier chapitre aborde le contexte historique et physiologique des mouvements fantôme, soulignant la sous-représentation du système nerveux périphérique dans ce domaine. Les recherches sur la réorganisation post-amputation révèlent un paradoxe : malgré l'existence de la mobilité fantôme le membre amputé n'est plus représenté dans le cortex. Cette thèse vise à résoudre ce paradoxe en examinant de nouveau le système nerveux périphérique. La première étude analyse les patrons d'activités musculaires dans le membre résiduel pendant les mouvements fantômes. La spécificité de ces patrons d'activité ne peut pas s'expliquer par la réorganisation corticale seule, mais suggère la formation de sous-volumes musculaires via une repousse neuronale préiphérique. L'étude suivante examine l'effet de l'entraînement sur la mobilité fantôme, confirmant qu'il améliore la capacité à mobiliser la main fantôme, tandis que les patrons d'activité EMG et donc les commandes motrices restent largement inchangés. La dernière étude utilise l'IRMf pour analyser la réponse corticale à l'entrainement et montre une différence significative de l'évolution de la dissimilarité dans la représentation des doigts entre intact et fantômes, surtout pour les mouvements ayant montré une amélioration comportementale. Cette thèse conclut à une probable réorganisation périphérique post-amputation pour expliquer la représentation du membre dans le système sensori-moteur. Les résultats suggèrent en effet la persistance de la commande motrice du mouvement fantôme dans le cortex moteur (M1), en parallèle d'une réorganisation périphérique, permettant ainsi d'activer des effecteurs et de fournir un retour somatosensoriel spécifique par la contraction musculaire et le mouvement des tissus. Ce travail offre de nouvelles perspectives sur la réorganisation du système nerveux après amputation et des implications pour les stratégies de rééducation visant à améliorer le contrôle des prothèses.

Mots clés: amputation, électromyographie, mouvement fantôme, IRM fonctionnel, entrainement somatosensoriel

Abstract and keywords

This thesis investigates the neurophysiological mechanisms underlying phantom hand movements in upper limb amputees, focusing on their notable slowness and difficulty of execution. It examines the outcomes of sensorimotor loop reorganization post-amputation and following daily sensorimotor-based home training. Phantom mobility, where amputees voluntarily move their phantom limb, serves as a key model illustrating the plasticity of the adult neural system. The first chapter reviews the historical and physiological context of painless phantom limb sensations, particularly phantom limb mobility, highlighting the long-standing underrepresentation of the peripheral nervous system in research on this phenomenon. The results of extensive research on amputation at the cortical level have revealed a paradox: cortical reorganization, in which the amputated limb's cortical representation is seemingly taken over by adjacent regions in the primary sensory (S1) and motor (M1) cortices, contrasts with the continued presence of phantom mobility. This thesis aims to address this paradox by closely investigating the peripheral nervous system.

The first study analyzes muscle activity in the residual limbs of amputees using surface electromyography (sEMG) during phantom movements, revealing that these movements involve actual motor execution through residual muscles, similar to intact limb movements. Crucially, the results suggest that the spatial specificity of these patterns cannot be explained solely by cortical reorganization but instead point to the formation of muscle subvolumes. The subsequent study examines the effects of training on phantom mobility, confirming that training improves the ability to mobilize the phantom hand, while the EMG patterns, and thus the motor commands, remain largely unchanged. The final study uses fMRI for cortical analysis to investigate changes in somatosensory feedback during phantom movements. The results show that training enhances the ability to differentiate between finger representations, particularly for movements showing behavioral improvement.

This thesis proposes a hypothesis of peripheral reorganization post-amputation to resolve the paradox regarding the representation of the limb in the sensorimotor system. The findings suggest the partial persistence of a motor command representing the lost limb in M1, alongside peripheral reorganization, which allows these motor commands to activate effectors and provide somatosensory feedback through muscle contraction and tissue movement. This work provides new insights into nervous system reorganization after amputation and offers potential implications for rehabilitation strategies aimed at improving control over phantom limbs in amputees.

Keywords: amputation, electromyography, phantom movement, fMRI, somatosensory training

Acknowledgements

Completing this PhD has been a long and rewarding journey, and it would not have been possible without the support and guidance of many people. I would like to take this opportunity to express my gratitude to everyone who has contributed to the successful completion of this work.

I am grateful to Jozina De Graaf without whom this project would not have existed. I would also like to extend my sincere thanks to Michel Akselrod, Hadrien Ceyte, and the members of my thesis committee, Fabrice Sarlegna and Christian Bénar for their valuable feedback, constructive criticism, and for fostering an intellectually stimulating environment. Their contributions have been essential to the development of this thesis.

Special thanks to my fellow PhD students, with whom I shared many discussions, ideas, and experiences during this journey. Your camaraderie and advice have been deeply appreciated. I am especially grateful to Claire Mahé for her assistance and support, both professionally and personally.

I would also like to acknowledge the administrative staff at ISM, whose support behind the scenes made it possible to navigate through the various stages of the PhD process smoothly.

On a personal note, I owe a debt of gratitude to my friends and family for their unwavering support and belief in me. To my childhood friends, your encouragement has given me the strength to pursue my ambitions. To my partner, Sally Maihoub, your love, patience, and understanding have been my anchor throughout this challenging period.

Finally, I would like to dedicate this thesis to my much-missed friend Audrey Coignard whose strength and kindness have inspired me all along.

Thank you all for your support.

Contents

Affidavit 2

Publications 3

Résumé et mots clés 4

Abstract and keywords 5

Acknowledgements 6

Contents 7

List of Figures 10

List of Tables 12

General introduction 13

I. Phantom mobility in its historical and physiological context 18

I.1. Epidemiology and characteristics of phantom limb sensations 18

I.1.1. A brief historic of phantom sensations 18

I.1.2. Epidemiology and characteristics of painless phantom sensations 20

I.1.3. Epidemiology and characteristics of phantom mobility 23

I.2. Theoretical framework and physiology behind intact hand movements 26

I.2.1. Somatotopy and plasticity in the central nervous system 26

I.2.2. The sensorimotor loop of hand movements 31

I.3. Amputation and its consequences on the sensorimotor loop : from literature findings to our hypothesis on mechanisms underlying phantom mobility 34

I.3.1. Amputation-triggered reorganization of the sensorimotor system 34

I.3.2. Phantom hand movement : real movement or figment of the imagination ? 36

I.3.3. How to reconcile post-amputation reorganization and phantom mobility ? 39

II. New insights into muscle activity associated with phantom hand movements 41

II.1. Introduction 41

II.2. Methods . . . 43
II.2.1. Participants . . . 43
II.2.2. Protocol . . . 45
II.2.3. Recordings . . . 46
II.2.4. Analyses . . . 48
II.2.4.1. Preprocessing . . . 49
II.2.4.2. Relative phasic muscle activity . . . 50
II.2.4.3. Movement-type and electrode-site specificities . . . 51
II.2.4.4. Statistics . . . 52
II.3. Results . . . 53
II.4. Discussion . . . 59

III. Phantom movement training without classifier performance feedback improves mobilization ability while maintaining EMG pattern classification 68
III.1. Introduction . . . 68
III.2. Methods . . . 71
III.2.1. Participants . . . 71
III.2.2. Protocol . . . 71
III.2.3. Recordings . . . 74
III.2.4. Analyses . . . 75
III.2.4.1. Kinematics . . . 76
III.2.4.2. EMG patterns . . . 80
III.2.4.3. Statistics . . . 83
III.3. Results . . . 83
III.3.1. Kinematics . . . 83
III.3.2. EMG patterns . . . 88
III.4. Discussion . . . 88

IV. Cortical correlates of the improvement of phantom movement perception after training 94
IV.1. Introduction . . . 94
IV.2. Methods . . . 96
IV.2.1. Participants . . . 96
IV.2.2. Protocol . . . 96
IV.2.3. Data acquisition . . . 97
IV.2.4. Analyses . . . 98
IV.2.4.1. Representational Similarity Analysis (RSA) . . . 99
IV.3. Results . . . 100
IV.4. Discussion . . . 104

General discussion 108

Bibliography 113

A. Use of MEG to localize motor commands and somatosensory feedback of phantom hand movements **i**

List of Figures

I.1. Penfield and Rasmussen's 1950 homunculi upon hemisphere crosssections. . . . 26
I.2. Schematic of putative cortical reorganization : unmasking 34

II.1. EMG electrode placements on the residual upper arm for the six amputees (P1 to P6) and one control participant (right side). 48
II.2. Illustration of EMG signal processing resulting in relative phasic muscle activity values. 50
II.3. Examples of schematic movement type, electrode site, and global specificities. 52
II.4. Sample of scaled EMG traces recorded on upper arms, showing the difference in specificity of signals between amputees and controls. . . 56
II.5. Relative phasic activity across movement types and electrode sites. . . 57
II.6. Movement-type and electrode-site specificity of the patterns of phasic activity. 57

III.1. Electrode placements on the residual limb of the 6 participants. . . . 75
III.2. Illustration of the reproducibility indices computation. 77
III.3. Fluidity index computation. 79
III.4. Kinematics performance before and after training 84
III.5. Relationship between amplitude and peak velocity for participant P5 . 86
III.6. EMG-related metrics before and after training. 87

IV.1. Color matrices of RSA between fingers in pre and post for participant P2. The difference post-pre between these matrices is also displayed. The 2D representation of these matrices are displayed below each matrix with the between-trial variability of the representation of each finger (ellipses represent the standard error of the mean (SEM)). The 2D representations show a change in dissimilarity D4-D5 bettween pre and post in phantom movement, which is also seen in the post-pre matrix. : the representation of these fingers overlapped before training and are represented as distinct after training. 102
IV.2. Boxplot of RSA values summed over fingers before training 103
IV.3. Compilation of summed RSA values between each finger Dx after training and all the other fingers before training. 103

IV.4. Boxplots for classified phantom movements according to the collected behavioural results. "Intention" : movement that the participants has never been able to perform. "Appeared" : movement that has appeared with training. "Improved" : movement which perception improved with training. "Stable" : movement that has not improved with training. . . 104

A.1. Hypothesis on the altered sensorimotor loop underlying phantom hand mobility iii

List of Tables

II.1. Demographic data concerning the six amputated participants. 44
II.2. Statistical analyses to compare muscle activity patterns during IHM and PHM using the relative phasic activity and its variability across movement-type and electrode-site. 58

III.1. Demographic data concerning the six amputated participants. 72

General introduction

Phantom mobility is an astonishing phenomenon in which individuals can voluntarily elicit sensations of movement in the phantom limb. It is perceived by a large majority of upper limb amputees and serves as a model of plasticity of the sensorimotor loop and the extend of its reorganization.

Interest in phantom limbs dates back to the 16th century, when Ambroise Paré first documented phantom sensations in amputees. Initially studied through the pain it elicited, this phenomenon was later studied more broadly in the mid-20th century as medical and scientific communities began to distinguish it from psychiatric conditions, recognizing it as a result of true physiological changes. Painless phantom sensations are in fact more common than phantom pain, with studies reporting a prevalence of 76% to 95% (Kooijman et al. 2000, Bachini et al. [n.d.] : under review). These sensations, which include proprioceptive (sense of presence and position) and exteroceptive experiences (itching, pressure, coldness or warmth), are influenced by various factors and are highly variable across individuals. In spite of their high prevalence, these painless sensations often remain underexplored in both fundamental and clinical research. Phantom mobility is a voluntarily provoked painless phantom sensation that is reported by no less than 76% of upper limb amputees (Touillet et al. 2018) and that can persist for decades post-amputation. It involves a variety of movements such as finger flexion/extension and wrist rotations. Despite the absence of the limb and thus any apparent physical constraints, the voluntary mobilisation of the

phantom limb requires significant concentration, effort, and is sometimes hindered by perceived resistance, as patients report.

Penfield and Boldrey were the first to privide a schema of the somatotopic organization in the primary sensory (S1) and motor (M1) cortices, where body parts are represented in proportion to their functional significance : larger cortical areas are dedicated to body parts requiring fine sensory processing or motor control (Penfield; Boldrey 1937,Penfield; Rasmussen 1950). In fact, while somatotopy in the primary somatosensory cortex (S1) indeed follows a sequential organization in tactile tasks (Roux et al. 2018), the primary motor cortex (M1) displays a distributed and overlapping representation of muscle groups, reflecting coordinated motor control rather than anatomical order (Sanes; Donoghue 2000; Schieber 2001; Marconi et al. 2007; Cunningham et al. 2013). Although these cortical representations were traditionally seen as fixed (Brugger 2005), later research demonstrated that the whole sensorimotor system, including the cortex, spinal cord, and basal ganglia, exhibits significant plasticity, allowing for functional reorganization in response to experience or injury (Leyton; Sherrington 1917; Liepert et al. 1999; Penfield; Jasper 1954; Nambu 2011; Zhang et al. 2010). The sensorimotor loop underlying intact hand movements integrates motor commands from the cortex with somatosensory and, possibly, visual feedback, facilitating precise control and adjustments. This loop, which involves reciprocal connections between various cortical and subcortical regions, is essential for complex hand functions, particularly those requiring fine motor skills. In cases where somatosensory feedback is disrupted, such as in amputees or deafferented patients, motor control is impaired, underscoring the loop's importance.

The physiological mechanisms that underly phantom mobility involve a sensorimotor loop that resembles the one involved in a movement of the intact limb. First, phantom hand movements, although not visible to an external observer, involve real motor execution, involving specific muscle contractions in the residual limb (Reilly et al.

2006; Jarrasse et al. 2017a; Jarrasse et al. 2017b). In addition, these movements activate similar brain regions as intact movements, suggesting a genuine sensorimotor loop and validating phantom mobility as more than just an illusion or motor imagery (Raffin et al. 2012b). Yet, amputation (i.e. major deafferentation and deefferentation) triggers extensive reorganization in the sensorimotor system. In particular, early studies suggested major remapping in the cortex , leading to a takeover of the lost limb representation by the adjacent representations in S1 and M1 (Pons et al. 1991; Florence; Kaas 1995). However, there is a paradox between cortical reorganization and phantom mobility : despite cortical reorganization erasing the cortical representation of the amputated limb, patients can voluntarily send motor commands to the phantom limb and perceive its movements. To explain this, Melzack proposed the "neuromatrix" theory, suggesting a hard-wired representation of the body persists in the brain (Melzack 1992). Reilly and Sirigu later hypothesized two overlapping maps in M1, with a preserved "motor command map" enabling phantom mobility (Reilly; Sirigu 2008). But these theories remain largely speculative and lack physiological evidence, which leaves the paradox unresolved.

Through the present thesis, my aim was to gain more insights into the neurophysiological mechanisms underlying phantom mobility to try to resolve the previously described paradox. By approaching the phenomenon through the angle of its surprising difficulty of execution and by taking into account all post-amputation reorganizational phenomena observed, and the ones occuring in the peripheral nervous system in particular, I attempted to reconcile phantom mobility with the apparent cortical remapping observed. Several studies on monkeys indeed indicate that sprouting at the periphery occurs after amputation, which might significantly contribute to the apparent cortical remapping. My focus on the peripheral nervous system was first conducted through the investigation into the nature of the patterns of activity in the residual limb during phantom hand movements (see Chapter II). We compared them

to analogous patterns of activity in the intact upper arm during analougous intact hand movements. To be able to pinpoint the neural correlate of difficulty of execution, we explored phantom movement training, which is known to reduce the difficulty of execution, in two other studies. In the first one of them (see Chapter III), we investigated the peripheral nervous system through the use of classification of muscle activity patterns. In the second one of them (see Chapter IV), we explored the cortical correlates, in particular in S1, using fMRI analysis during phantom finger movements. Finally, in the last part of my thesis, I wanted to more directly study the link between cortical activity during phantom hand movements and peripheral muscular activity systematically associated to it. According to our hypothesis, muscle activity on the residual upper arm of transhumeral amputees during phantom hand movements should correlate with motor commands comming from the hand area of the cortex but a somatosensory feedback resulting in activation in the arm area of S1, at least in part, thus resulting in an altered sensorimotor loop. Because no workable result could be extracted from it, the rationale behind this study and the discussion on its failure are detailed in Appendix A instead of occupying a full chapter.

I initially aimed to focus this thesis exclusively on participants with transhumeral amputations to ensure a homogeneous level of amputation for group statistical analyses. Additionally, different levels of amputation involve distinct physiological backgrounds, which is crucial to take into account for interpreting the results. In transhumeral amputees, all muscles directly involved in intact hand movements, including the extrinsic muscles of the forearm, are removed by the amputation. This contrasts with transradial amputees, where some of these muscles remain intact or only partially damaged. As a result, for transhumeral amputees, the intact sensorimotor loop is completely disrupted and cannot be utilized in phantom hand mobility. However, the recruitment of amputees proved more challenging than anticipated, and we had to include transradial amputees as well. Consequently, throughout the thesis, I have

differentiated the discussion of results between these two categories of participants when necessary.

I. Phantom mobility in its historical and physiological context : from delusion to “real movement of a dematerialised limb” [1]

I.1. Epidemiology and characteristics of phantom limb sensations

I.1.1. A brief historic of phantom sensations

Although the terminology did not exist at the time, interest in what we now call "phantom limbs" began in the medical field as early as the 16th century, and probably even before in medieval texts under the disguising term of “miracles” (Wade 2009). Specifically, the first recorded instance of phantom sensations in literature arose when the French surgeon Ambroise Paré transitioned from using cauterization to ligatures during amputation surgery. This resulted in a higher survival rate, providing an opportunity to learn from patients’ experiences. Interestingly, Paré’s knowledge about sensations existing in the lost limb also allowed him to be alerted by similar

[1] cited from the review published by Scaliti and colleagues in 2020

sensations reported even before surgery, where patients experienced pain from dead tissues once affected by gangrene. Ambroise Paré believed that the pain felt was merely "the strong apprehension of great paine which formerly reigned in the part" (Paré 1575) i.e., the memory of pain before the tissues died. His aim was to raise awareness about this phenomenon among young surgeons : these painful sensations, mislocalized as coming from dead tissues, should not deter them from amputating the limb when it represents the only decision that can save the patient's life. In the 17th century, René Descartes used sensations in the lost limb as an argument supporting his theory stating that all sensations are localised in the brain and not in the peripheral tissues directly. Throughout History, other surgeons and scientists, such as Aaron Lemos, Johannes Muller, and Charles Bell, provided clinical descriptions of sensations reported by patients as originating from the lost limb. Sir Weir Mitchell finally coined the term "phantom limbs" in the fiction "The Case of George Dedlow" (Mitchell 1866) where the exposed events were based on his experience as a surgeon. In this fictional story, a former soldier who had lost all four limbs felt "pain in both legs". As explained by Finger and Hustwit, each of these scientists offered their own insights about the phenomenon and their own hypotheses about its origins (Finger; Hustwit 2003). Although the general term "phantom limbs" is used in the above-mentioned review article, all these accounts primarily referred to phantom pain in particular. Admittedly, Charles Bell mentioned "a sense of [the lost limb's] position", but it was described as occurring through pain. Similarly, through George Dedlow's fiction, Sir Mitchell wrote about 'the sense of having that limb' but it 'faded away entirely' when pain disappeared. Putting pain at the chore of reports on phantom sensations may have been a deliberate choice as in the clinical context, pain is naturally considered as a symptom to be treated and thus taken more seriously than any other painless sensation, both by patients and caretakers. When patients dared to mention their painless sensations, they were considered as "delusional" (Mitchell 1872), as a sign of the non-acceptance

that the limb is now gone. Because "disbelief" and even "accusations of insanity" (Riddoch 1941) coming from the medical body were feared by patients, accounts were lacking and painless phantom sensations could not be investigated further. Thus, the main focus on pain lasted for many years and it is only in the mid 20th century that more comprehensive reports on a larger scope of phantom sensations were published (Riddoch 1941; Henderson; Smyth 1948). These surgeons wanted to clarify the fact that the phenomenon of phantom limbs that affects amputated patients is entirely different from "phantom-illusions" encountered as symptoms of psychiatric conditions such as "insanity" or "hysteria" for there is no "mental disturbance" involved in the phantom sensations at stake. Through their impulse, they wanted to allow patients to speak more openly about their phantom sensations, embodying the first step towards phantom sensations truly being investigated by the scientific and medical communities, hand in hand, as an illusion arising from real physiological changes. Nowadays, even if painless phantom sensations are not systematically taken into account in rehabilitation processes, they are studied by researchers in the context of plasticity in the adult nervous system (Giraux; Sirigu 2003; Makin et al. 2015; Kikkert et al. 2016).

I.1.2. Epidemiology and characteristics of painless phantom sensations

While phantom limb pain may indeed be prevalent, it only represents one facet of the reported sensations. Indeed, researchers reported a prevalence of painless sensations in upper limb amputees of 76% (55 our of 72) and 92% (70 out of 76), respectively in Kooijman et al. 2000 and Touillet et al. 2018. For lower limb amputees, the prevalence reaches 95% according to Bachini et al. [n.d.] (under review). In fact, these results make painless phantom sensations more prevalent than phantom pain (Sherman

et al. 1984; Kooijman et al. 2000). The painless phantom is unique to each patient in terms of type, localization, and intensity, with various factors reported to influence it in different ways. In spite of this diversity, in the following, I chose to deliver a description of the most common features of painless phantom sensations so that the reader can grasp a tangible sense of it.

Proprioceptive sensations of the phantom typically appear directly after amputation, as soon as when the patient wakes up from surgery, most of the time as a sense of presence. Giummarra and colleagues found that among the 283 amputated participants studied, the group of amputees that felt only the distal part of their amputated limb (i.e. hand or foot) and the group that felt the whole phantom limb were about the same size i.e. almost 50% because the participants who only felt the proximal part were very rare (Giummarra et al. 2010). Yet, in upper limb amputees in particular, according to my experience and to other sources (Touillet et al. 2018; Henderson; Smyth 1948; Brugger 2005), it is the distal part (i.e. the hand) of the phantom, either whole or partial (only a few fingers or the thumb) that is most often felt. Regardless of the different distributions of partial sensation along the limb, phantom perception of presence usually strongly resembles the proprioceptive sensation that can be felt from an intact limb. It is felt constantly unless the amputee engages in activities that redirect their attention, a phenomenon also observed with intact body parts, whether the individual is an amputee or not. Regarding the position of the phantom, only one patient that I have encountered describes the sense of presence without being able to localise his phantom hand in space. The hand is reported as detached from the stump and localised “somewhere around here”. In most cases however, the position is clearly reported. The phantom usually has a normal orientation and position in accordance with the stump’s own position and it follows stump movements (Ramachandran; Hirstein 1998). Yet, in some cases, the phantom fingers or toes are curled or clenched, sometimes taking anatomically impossible postures such as the

fingers being stuck inside the palm or the limb taking a twisted position in relation to the stump (Giummarra et al. 2010). Also, the phantom hand has been found, in a non negligible part of upper limb amputees, as gradually approaching the stump from its normal position within the first six months after amputation (Jensen et al. 1983). This phenomenon, referred to as "telescoping", ultimately resulted in either the phantom "disappearing [inside the stump] and fading away" (Riddoch 1941) or a telescoped phantom hand that remained attached to the stump with sometimes only fingers sticking out (Ramachandran; Hirstein 1998; Giummarra et al. 2010). In the latter telescoped case, if the amputee had previously felt their phantom elbow and wrist, it was not the case anymore ; like a retracted telescope, all the articulations had vanished. Yet, sensations related to the remaining phantom hand have been reported several decades after amputation (Touillet et al. 2018). When the amputee with a telescoped phantom limb puts a prosthetic limb on, it happens that the phantom hand or foot changes location to coincide with the prosthetic hand of foot, without getting the articulations back (Giummarra et al. 2010). When it comes to the shape of the phantom, it resembles the one of the intact limb most of the time (Giummarra et al. 2010). Quite rarely, it is reported as abnormal : bigger (sometimes felt as "inflated") or thinner. For example, one of Riddoch's patients had a phantom foot that "seems to be broader than the other".

In addition to the previously described proprioceptive sensation of presence, exteroceptive sensations have also been outlined. They are very diverse and expressed uniquely in each participant : itching, creeping of ants, pressure (as if their phantom limb was caught in a vice), touch (as if someone was touching their phantom limb), and temperature. I would also add referred sensations to this category but they are a bit particular because they can manifest through any of the above-mentioned sensations, only they are elicited through tactile stimulation in specific locations of the stump or the face (Brugger 2005).

Finally, various external or internal factors were reported to influence these painless phantom sensations : the weather, emotions, the state of mental health, fatigue etc... and the nature and intensity of this influence is specific to the patient (Bachini et al. [n.d.], under review). Yet, it is mostly the attention given to the phantom limb that modulates its intensity.

Painless phantom sensations are frequently experienced passively, with patients seldom able to exert control, and rather compelled to endure the effects of various external factors beyond their volition. Consequently, except for epidemiology and statistical studies that are useful to the medical community for monitoring and rehabilitating patients with prosthetic limbs, such painless phantom sensations are rarely investigated. However, there exists an active painless phantom phenomenon called 'voluntary phantom mobility' (Giummarra et al. 2010; De Graaf et al. 2016; Touillet et al. 2018). This phenomenon has raised increasing interest in recent years and will be the central focus of this thesis.

I.1.3. Epidemiology and characteristics of phantom mobility

Voluntary phantom mobility is better described as an ability than a mere sensation. I found the first clear account of such a case in Riddoch's acticle (1941) where a patient could "on voluntary effort, [..] flex and extend the phantom foot and toes" (Riddoch 1941). Both perception and control of phantom movements are reported as resembling those of intact limbs : this is a natural ability (De Graaf et al. 2016). In the most recent reports, while only 47% (132 out of 283) of both upper and lower limb amputees reported to be able to voluntarily elicit phantom movement sensations (Giummarra et al. 2010), the prevalence reached 76% when our team focused on upper limb amputees exclusively : 58 out of the 76 patients could perform phantom hand and wrist movements (Touillet et al. 2018). Since the puplication of this article, in spite

of the additional participants, the prevalence remained stable. Touillet and colleagues demonstrated persistence of phantom mobility over many years. Out of the 58 participants with phantom mobility, 22 (38%) had their amputation surgery more than one decade ago, with one individual having undergone amputation as far back as 40 years prior. Some participants even discovered their phantom mobility during their interview with the researchers, years after amputation was performed. In the same study, nine distinct types of phantom hand movements (PHM) were reported : global hand opening/closing, flexion/extension of individual fingers, pinch grip closing/opening, flexion/extension of 2 to 3 undissociated fingers, and abduction/adduction of fingers. Additionnally, researchers identified all the potential movements of the wrist in the reports of phantom movements : flexion/extension, ulnar/radial inclination and prono-supination. Similarly to what can be described for other types of phantom sensations, participants' abilities vary considerably. Some participants could perform all of the above-mentioned movements, while others only a few even if they could feel all five fingers at rest. Some could perform individualised movements of fingers while others were only able to make a fist. Overall, forearm amputees had more "mobilization capacity" (i.e. higher number of executable phantom movements) than upper arm amputees. In terms of velocity and amplitude, phantom hand mobility is variable accross subjects but also across movement types within the same subject (Touillet et al. 2018; De Graaf et al. 2016). However, several common features can be noted. First, phantom movements require profound concentration which is associated with fatigue, amputees feeling as if their hand is caught in a vice and their fight against it sometimes provoking sweating and eventual blocking (i.e. the phantom limb is perceived as paralyzed). It is important to note that this struggle is not associated with phantom pain and often occurred only for certain types of movements, the nature of which depended on the patient. Second, probably being a consequence of the first, these movements typically occurred at notably reduced velocity compared to intact

hand movements under similar conditions.

These two features raised our particular interest because we had anticipated that the absence of the limb would eliminate any physical limitations. Therefore, they offer an intriguing perspective for delving into the physiological mechanisms underlying phantom mobility, particularly the reorganization of the sensorimotor loop and thus its plasticity in the adult central and peripheral nervous systems. In the following sections, I will discuss the advances that have contributed to our current understanding of the reorganization of the nervous system following amputation, leading to the particular sensorimotor loop involved in phantom mobility.

I.2. Theoretical framework and physiology behind intact hand movements

I.2.1. Somatotopy and plasticity in the central nervous system

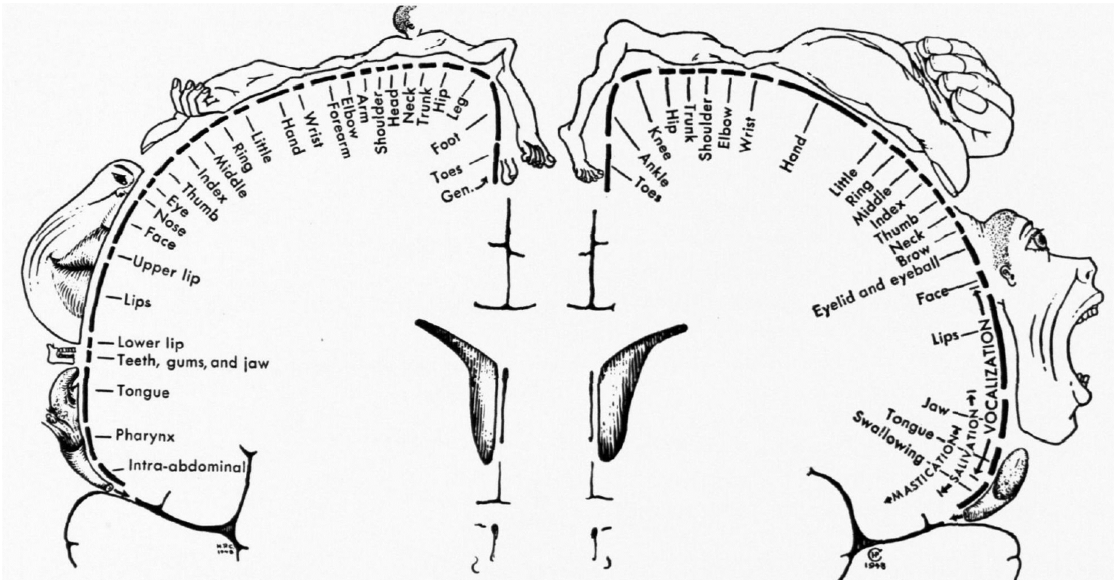

Figure I.1.: Penfield and Rasmussen's 1950 homunculi upon hemisphere crosssections. On the left is the somatosensory homunculus and on the right is the motor homunulus. This figure is adapted from Fig. 17 (left) and Fig. 22 (right) of the corresponding paper, and it illustrates a somatotopy in the functional representation of the body in its somatosensory and motor modalities.

Penfield and Boldrey, in 1937, were the first to finely describe the functional representation of the human body in the Rolandic area of the cortex : the primary somatosensory cortex (S1) in the postcentral gyrus (Brodmann areas 3,1 and 2) and the primary motor cortex (M1) in the precentral gyrus (Brodmann areas 4 and 6aα; Penfield; Boldrey 1937). To construct this cortical mapping, the two neurosurgeons conducted intraoperative electrical stimulations on the cortical surface of epileptic and cancer patients. They observed any resulting movements and prompted the patients to verbally communicate to localise their sensations. They later illustrated the observed cortical organization of movements and sensations with the use of a distorted human-like

figure called the homunculus, where each part's size proportionally reflected the cortical surface area dedicated to this specific body part. For instance, the hands, the face and the tongue of the somatosensory homunculus are "magnified" (Florence; Kaas 1995). In other words, they appear disproportionately larger than their anatomical counterparts because their representation within S1 is proportionally broader than on the body surface. Penfield's homunculi have become famous over the years because they have been very good ways to popularise complex mapping results to the lay audience. In fact, they had the purpose of being "aids to memory" (Penfield; Jasper 1954) to medical students. However, for further fundamental scientific research, it should be treated very cautiously. First, as pointed out by Zina Ward in her "Letter to the editor : Reexamining Penfield's Homunculus" (Ward 2014), Penfield's homunculi are ill scaled because the cortical surface in S1/M1 dedicated to a specific body part is not represented by the volume of the corresponding part on the homunculi. Instead, even though it is very unnatural for one's eyes, it is only the lengths on the rostrocaudal axis of the homunculi that correlate with the cortical surfaces. Thus, to avoid misleading the reader, I chose not to show the homunculi by themselves but rather the 1950 drawing which depicts the creature's body parts directly over the cortices (Penfield; Rasmussen 1950, see Figure I.1). Second, while the technique of cortical electrical stimulation is still widely used in surgery as a tool to avoid removal of any critical brain region, the way motor mapping was performed at the time became controversial in the following decades. Indeed, to adequately map the effectors of the stimulated cortical motoneurons, one should not rely on the subjective and indirect visual expression of their activation (i.e., the induced movement) but rather on muscle contraction itself in which case the true effectors, i.e., the muscles, can be more precisely pinpoint (Sala 2018; Taniguchi et al. 1993). Finally, it is essential to emphasise that while the point-to-point sequential mapping illustrated by the somatosensory homunculus accurately reflects S1 organization (Roux et al. 2018),

the organization in M1 is markedly different. While the major body parts (leg, arm and face) are indeed quite independently represented, the within-limb somatotopy in M1 is not sequentially ordered according to anatomy but rather reflects a distributed system. The representation of muscles in M1 are widely distributed within each major region, displaying large overlaps (Sanes; Donoghue 2000; Schieber 2001; Marconi et al. 2007; Cunningham et al. 2013). These overlaps could in part be explained by the fact that one movement rarely involves only one muscle and that as a consequence different movements have some muscle contractions in common. In fact, the overlapping organization found in M1 was called "functional somatotopy", suggesting that the distinct part of a muscle representation reflects individuated control while the overlapping part reflects the ability to contract several muscles coordinately (Plow et al. 2010). In 2017, Massé-Alarie and colleagues even demonstrated that different motor functions (i.e. execution of extension versus flexion of the wrist) could induce a shift in M1 excitability within a given forearm muscle's representation, when compared to rest (Massé-Alarie et al. 2017). This peculiar functional representation in M1 is inherently related to an anatomical feature that was unknown when Penfield's homunculi first emerged : divergence of the corticospinal pathway. Shinoda and colleagues indeed revealed, thanks to horseradish peroxidase (HRP) staining of motoneurons in M1, that each pyramidal neuron can innervate several spinal motoneurons from different pools which can even span several spinal segments (Shinoda et al. 1981). The functionnal significance of such a divergent anatomy was later demonstrated by several research groups thanks to the development of spike-triggered averaging of rectified EMG signals (Buys et al. 1986; Lemon et al. 1986; McKiernan et al. 1998).
Nevertheless, in terms of functional significance, cortical mapping of the body still holds considerable importance. Specifically, the proportion of pyramidal neurons within the primary somatosensory cortex (S1) dedicated to processing information from a particular body part yields valuable insights into that body part's sensitivity.

From an anatomical standpoint, this proportion reflects the degree of innervation that a specific region of S1 receives from the corresponding body part, which in turn reflects the density of mechanoreceptors present in the skin. For instance, the ability to precisely localise tactile stimuli on the fingertips stems from the high concentration of particularly small mechanoreceptors in this area, associated with small receptive fields, and leading to proportional enlargement of these body parts within S1. Similarly, the proportion of pyramidal neurons within the primary motor cortex (M1) devoted to controlling a specific body part offers indications regarding the range and precision of movements achievable. From an anatomical standpoint, this proportion reflects the degree of innervation that M1 provides to a specific body part, which in turn reflects the density of motor units used. For example, hand movements, which are very diverse and precise, are controlled by a proportionally large region of M1 compared to other body parts. Their precision is explained by the fact that each pyramidal neuron innervates a small number of spinal motoneurons (smaller compared to movements of other body parts) that in turn innervate a small number of muscle fibres, thus forming small motor units and eventually allowing precise control of the produced force.

The adult sensorimotor cortex, and more generally the adult brain, has long been considered resistant to functional reorganisation and it was still an “axiom of neuroscience” in the 1980s (Brugger 2005). In other words, the representation of the body within the cortex was thought to be unalterable. However, several researchers have proved it wrong. As early as 1917, Leyton and Sherrington found that repetitive stimulation of the sensorimotor cortex elicited changes in movement responses, such as facilitation, reversal or deviation [2] (Leyton; Sherrington 1917). Even more inter-

[2] Leyton and Sherington mentioned in their publication "facilitation", "reversal" and "deviation" as the 3 concrete examples of "functional instability of cortical motor points" revealed through cortical stimulation. This instability corresponds to changes in motor responses after repeated stimulations

esting is to explore what happens in more ecological conditions i.e., when a patient or participant is no longer passive but active. In this context, cortical representation of the body has been shown to be flexible, that is to say transiently alterable. For example, Liepert and colleagues asked their participants to repeat for 40 minutes some movements of the thumb and foot in a synchronous manner (Liepert et al. 1999). Using TMS, they showed that after training, a medial shift of the thumb representation in M1 towards that of the foot occurred and lasted up to one hour. This flexibility is revealed even through more simple movements such as thumb unidirectional movements (Classen et al. 1998). Additionally, and even more importantly in respect to adaptation capabilities, cortical representation of the body can undergo long term adaptations : the cortex is plastic. Xerri and colleagues have shown that 58 days after eliciting a stoke in S1 hand knob region of a monkey, the functional representation was reconstructed on the side of the lesion after transiently disappearing (Xerri et al. 1998). This progressive reorganization involved in the reconstruction of the functional representation paralleled with behavioural improvements.

Yet, the cortex is not the only location of the central nervous system where somatotopic arrangements dwell. First, it has been known and accepted for a long time that somatosensory and motor information are processed in segments of the spinal cord that are specific to the body part involved. Second, although less explored and less precise, somatotopy also exists in the sensory thalamus (Penfield; Jasper 1954) as well as in the different nuclei of the basal ganglia (Nambu 2011). The basal ganglia, composed of the striatum, the subthalamic nucleus, the globus pallidus, the substantia nigra and the motor thalamus, are involved in motor control. Body representation in some of these structures is also plastic. For example, after brain injury induced in M1,

of the motor cortex, taking as reference the result of the first stimulation. Facilitation corresponds to an increase of movement amplitude. Reversal corresponds to a complete change of the direction of the movement, where flexion becomes extension and vice versa. Deviation corresponds to a change in the nature of the movement e.g. a different joint is involved.

reorganization through axonal sprouting has been found in the spinal cord of adult mice and rats, and paralleled with functional recovery (Lapash Daniels et al. 2009; Zhang et al. 2010). Thus, plasticity appears as a major characteristic of not only the cortex but also the spinal cord and likely the whole sensorimotor system.

I.2.2. The sensorimotor loop of hand movements

Every limb movement entails a distinct sensorimotor loop, which is a concept that delineates the dynamic interplay between motor control and sensory processing of, among others, somatosensory and visual feedback of a given action. For instance, in hand movements, the sensory feedback can include visual perception of the body parts in motion and more importantly the "muscle sense" (Wade 2009) that the limb is moving (i.e. proprioceptive feedback). These sensory inputs will, in real time, influence motor outputs and vice versa, forming the feedback loop that is crucial for fine-tuned movements.

Hand movements, because of their particular prevalence in mobility of the phantom upperlimb and their functional interest in everyday life, are the movements that will be at the chore of this thesis. Schematically, the sensorimotor loop at stake during *hand movements* is organized as follows :

> *Motor commands for a specific hand movement originate from active cortical motoneurons distributed throughout the upper limb region of M1. These commands ultimately activate the muscles fibers required for the hand movement, including the ones in postural trunk muscles and upper arm muscles that maintain the position of the proximal part of the limb during such distal movements. Action potentials propagate through the corticospinal tract, which is the main descending motor pathway in primates*

and where pyramidal neurons directly innervate the spinal cord. There, spinal motoneurons are activated, eventually leading to the contraction of muscle fibers via the peripheral muscular junction. Because the descending motor tract is both divergent and convergent, each cortical motor neurons innervates several spinal motoneurons and conversely, each spinal motoneuron is activated by several cortical motor neurons. The activation of mechanoreceptors, triggered by the consequent tissue movement (muscles, tendons, and skin), gives rise to somatosensory feedback ending in a specific region of S1 (for the majority of them) after passing through several synapses in the brain stem and thalamus.

However, when one mentions a loop, the reality lies closer to a complex network with ramifications at each level. Indeed, the sensorimotor loop is controlled through feed-forward inhibition coming from collaterals at each synaptic relay, as well as through reciprocal connections between M1 and other cortical and subcortical regions such as S1, the thalamus, the putamen and the pons (Catani et al. 2012). This architecture is essential to the immediate control of precise movements, through the constant ongoing control of the motor input amplitude.

The hand can perform the largest variety of movements of any body part. This is due to its complex anatomy, which includes numerous muscles and joints, resulting in 27 degrees of freedom[3] (DOF; Husain 2022). In comparison, the foot has 23 DOF (Olinski et al. 2015). This anatomical complexity implies a complex control of movements as well, in particular for movements of precision that rely highly on online

[3]The number of degrees of freedom refers to the number of independent ways a limb can move across different planes. Each degree of freedom represents a separate type of movement, such as flexion/extension (bending and straightening) or rotation. For example, a human finger has multiple degrees of freedom: at the knuckle (metacarpophalangeal joint), the finger can flex/extend (bend and straighten) and move side to side (abduct/adduct), while at the middle and distal joints, the finger primarily flexes and extends.

somatosensory feedback. This was highlighted through the study of proprioceptively deafferented patients such as patient G.L., who lacks somatosensory feedback up to the neck but is still able to perform complex motor tasks under visual control, although with more difficulty and slower than for non-deafferented individuals. Intact somatosensory feedback has been shown to be essential to determine the onset of coordinated movements (Bard et al. 1992), to control grip force during object manipulation (Nowak 2004), but not to perform ballistic reaching tasks (Sarlegna et al. 2006). Neural correlates of the absence of somatosensory feedback have been found in the contralateral sensorimotor cortex during precision grip : the patient's functional alpha band network is altered (Patino et al. 2006). Thus, in cases of alterations of the somatosensory feedback due to reorganization of the nervous system caused by injury, an altered version of the sensorimotor loop is involved in movement, with both behavioural and neural evidence.

I.3. Amputation and its consequences on the sensorimotor loop : from litterature findings to our hypothesis on mechanisms underlying phantom mobility

I.3.1. Amputation-triggered reorganization of the sensorimotor system

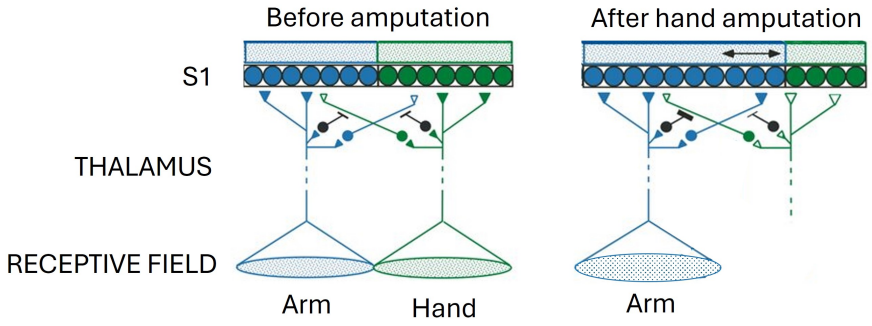

Figure I.2.: Schematic diagram illustrating unsmasking of thalamic secondary projections to the primary somatosensory cortex (S1) after deafferentation induced by amputation of the hand.

As discussed in section I.2.1, both stroke and repetitive movement can induce reorganization within the sensorimotor cortex. But what happens after major amputation? It is noteworthy that, unlike stroke, amputation involves a peripheral nerve lesion instead of a central lesion. Yet, deafferentation and deefferentation have been shown to induce reorganization at various levels of the nervous system. Cortical reorganization was identified in the non-human primate after transection of the mixed median nerve which innervated the palm of fingers D1 to D3 (Merzenich et al. 1983), after deafferentation of the forelimb through transection of dorsal roots in several spinal segments (Pons et al. 1991), or after amputation of a finger (Merzenich et al. 1983;

Rasmusson 1982; Calford; Tweedale 1991), or arm (Florence et al. 1998). However, interpretations of these cortical reorganisations with regard to the underlying physiological mechanisms have diverged. Merzenich and colleagues have reported, using peripheral tactile stimulation, that after transection of the median nerve, sensory inputs from the face, which cortical representation in S1 adjoined the deafferented area before amputation, also elicited activation in the deafferented part (Merzenich et al. 1984). While the rest of the deafferented cortex remained silent, the "reoccupation", studied until 22 days post-amputation, was limited to 1 to 2 mm. It was interpreted as an "upper limit" imposed by the medio-lateral span of the axonal projections of single thalamocortical neurons within S1. Following deprivation, the thalamocortical input predominantly projecting to the adjacent region in S1 would reveal its secondary projections towards the deafferented part (see figure I.2). Comparable shifts were observed in M1 (Jacobs; Donoghue 1991; Huntley 1997), interpreted akin to the unmasking phenomenon, particularly given the rapidity of remapping, occurring within weeks post-surgery. This remapping was attributed to the emergence of horizontal within-M1 excitatory connections previously silenced by feedforward inhibition. See figure I.2 for an illustration of unmasking in the somatosensory system. Pons and colleagues were the first to investigate the consequences of long-lasting deafferentation of a large part of the forelimb, through transection of the dorsal roots in several spinal segments (Pons et al. 1991). They described reorganisation of the somatosensory cortex at a much larger scale, with a practically complete reactivation of the deafferented area. These findings compelled the scientific community to reevaluate their hypothesis regarding the mechanisms underlying cortical reorganisation after amputation. They prompted a consideration of neural sprouting, which embodies reorganization on a larger scale than unmasking, to be regarded as a potential additional process (Pons et al. 1991; Florence; Kaas 1995). As a support to this hypothesis, sprouting has also been found in the primary visual cortex after retinal lesions in cats (Darian-Smith;

Gilbert 1994).

Cortical reorganization after amputation has been investigated very extensively but Florence & Kaas found that reorganization can also occur at other levels of the adult nervous system and account for the observed remapping at the level of the cortex (Florence; Kaas 1995). Using anterograde staining through bilateral injections in the arm and forearm of unilaterally amputated monkeys, they observed axonal sprouting in the spinal cord. They found similar anatomical proofs of reorganisation in the cuneate nucleus and interpreted these as a cause of major reorganisation through invasion of neighbouring areas previously depicted in S1.

Since the development of neuroimaging and electrophysiological techniques on the brain, the peripheral nervous system has thoroughly been ignored. However, the study of Manger and colleagues explained how apparent cortical remapping can occur through hyperinnervation[4] of the stump skin, caused by sprouting of severed spinal neurons that innervated the lost limb before amputation (Manger et al. 1996). In addition, more recent studies have described axonal sprouting of severed spinal motoneurons, targeting severed muscle volumes within 2 years after amputation (Wu; Kaas 2000). All of these findings have not been taken into account in the interpretation of apparent shifts observed in the cortex and this is starting to be called into question within scientific circles (Makin; Krakauer 2024; Schone et al. 2023).

I.3.2. Phantom hand movement : real movement or figment of the imagination ?

Schwartz defined voluntary movement as “a result of signals transmitted through a communication channel that links the internal world in our minds to the physical world around us” (Schwartz 2016). Yet, during voluntary movements of the phantom

[4]The tip of the stump shows a density of innervation comparable to that seen at the tip of an intact finger and higher that that seen at more proximal locations

limb, the external observer cannot witness any expression of movement in the physical world because the limb has been amputated. Without empirical evidence in the "physical world", the phenomenon does not fit the aforementioned definition of actual voluntary movement. Due to the concurrent experience of kinaesthetic sensations and absence of actual movement of the limb, phantom mobility has historically been considered by scientists as an "illusion of [ability]" as expressed by neurologist George Riddoch in his 1941 article, or at best, as "motor imagery" (Rosén et al. 2001; MacIver et al. 2008). However, the sensations of phantom movement, reported by amputees to be voluntary, intuitive and natural, resemble those experienced during intact movements (Reilly et al. 2006) while distinguishing themselves from those experienced during motor imagery of similar movements (Giraux; Sirigu 2003; Raffin et al. 2012a). This suggests that their validity extends beyond mere illusion. To be able to provide tangible support to these reports, several researchers have investigated the neural correlates of phantom movements. They identified several primary components that now enable the scientific community to consider phantom movements as "the real movements of a dematerialised [limb]" (Scaliti et al. 2020). First, during phantom hand movement (PHM) execution, Dhilon and colleagues recorded activity in severed peripheral motor nerves which used to innervate the amputated limb (Dhillon et al. 2005). Moreover, there may be no displacement of the limb in space, stump muscles systematically contract during phantom movements; the first detailed account of this dating back to 1948 in an article of Henderson and Smyth. For the more "distal amputations" (e.g. hand disarticulation, or toes and fingers amputations), stump contractions occurred in the remaining part of muscles that were already directly involved in the movement of the hand or foot before amputation (Henderson; Smyth 1948). Several other studies later recorded these muscle activities during different types of phantom hand and wrist movements in both transhumeral and transradial amputees (Gagne et al. 2009, Reilly et al. 2006). For a given patient, the patterns of activity in the residual arm are specific

to the type of phantom movement, even in the case of proximal amputation such as transhumeral amputation where the residual muscles were not directly involved in hand and wrist movements prior to amputation (Reilly et al. 2006; Jarrasse et al. 2017a; Jarrasse et al. 2017b). These findings indicate that phantom movement phenomenon involves a form of motor execution through activation of muscle effectors on the residual limb. Specific motor commands corresponding to the specific phantom movement that the participant intends to perform recruit muscle effectors in specific patterns. Thus, phantom mobility is entirely distinct from motor imagery and this is what is reaffirmed in Raffin and colleagues' fMRI study (Raffin et al. 2012b). They compared activation in a variety of brain areas between PHM and motor imagery of the amputated hand and found stronger activation of the primary motor and sensory cortices, the SMA, the dorsal premotor cortex and the anterior lobe of the cerebellum during phantom movement compared to motor imagery. These activations resembled those found during execution of movement in an intact limb. Moreover, an ischaemic block, leading to a dysfunction of the sensory fibers in particular, lead to an increasing difficulty in moving the phantom or to a totally frozen phantom depending on the participant, while the EMG patterns of activity persisted (Reilly et al. 2006). This indicated that the sensation of movement results from sensory feedback comming from contractions and tissue movements in the residual limb and not from cortico-cortical corollary discharge as sometimes argued (Subramanian et al. 2019). Together, these findings show that during phantom movements, a sensorimotor loop is involved and resembles the one of intact movements, even if the contraction of muscle effectors on the stump do not lead to any actual movement of a limb in space. Thus, I define phantom mobility as the natural ability to send specific motor commands to the phantom limb that will in turn elicit the somatosensory sensation of a movement through specific contractions of stump muscles.

I.3.3. How to reconcile post-amputation reorganization and phantom mobility ?

Phantom limbs, and phantom mobility in particular, face a paradox in the context of reorganization after amputation. On the one hand, as shown in section I.3.1, both the somatosensory and motor cortical regions formerly dedicated to the amputated limb, are taken over by neighbouring regions after amputation. On the other hand, phantom mobility is an ability experienced by a wide range of patients which involves an actual sensorimotor loop where motor commands are voluntary sent to elicit somatosensory sensations in the phantom limb through involuntarily and naturally reaching muscle effectors in the residual limb. This implies that the lost limb is still represented in the cortex. Several research groups tried to desentangle this paradox. First, Melzack theorized a large hard-wired brain network that he called "the neuromatrix". It would "continuously generate a characteristic pattern of impulses indicating that the body is intact", which was coined by Melzack as "the neurosignature" (Melzack 1992). This way, somatosensory information coming from the stump and holding information about the fact that the limb has been amputated would come into conflict with this neurosignature and would be rulled out as an error, allowing for phantom sensations to be felt. However, this theory does not consider the large reorganization that occurs throughout the nervous system and lacks both details and possibilities to be tested and to collect physiological evidence. Thus, in a second attempt to resolve the paradow, Reilly and Sirigu hypothesized that two interacting levels of representation superimpose in M1 : the "muscular map" and the "motor command map" (Reilly; Sirigu 2008). The "muscular map" would be the map that reorganizes after amputation while the integrity of the "motor command map" would allow for phantom mobility to exist. They take the example of PHM where the hand representation is not deleted by the takeover of neighbouring regions but persists under a slightly altered form.

The hand region of M1 would send motor commands to proximal remaining muscles through preserved descending pathways for muscles already involved in the movement before amputation or through "reactivated functionnal connections" for more proximal muscles. This hypothesis is supported by hand transplant studies where the representation of the hand quickly "reappears" after transplant (Giraux et al. 2001), indicating that the blueprint of the hand representation had been preserved all along. The problem with this hypothesis is its theoretical nature that does not propose any physiological mechanism that could explain the maintenance of the "motor command map" after amputation. Indeed, the "motor command map" appears quite intangible and Reilly and Sirigu's attempt to reconcile phantom mobility and post-amputation reorganization lacks physiological roots.

In the following chapter, we will take a closer look at the peripheral nervous system by examining the activity patterns associated with phantom mobility. Starting from the phenomenon of phantom mobility itself and its functional muscle correlates, we aim to provide broader insights into neural reorganization, keeping all possibilities open.

II. New insights into muscle activity associated with phantom hand movements

II.1. Introduction

Muscle activity in the residual limb associated with phantom mobility provides key evidence that phantom mobility involves an actual sensorimotor loop. Alongside the involvement of brain areas specialized in motor execution and control (Raffin et al. 2012b), it has been found that muscles in the residual limb act as effectors in these invisible movements. The contraction of these muscles, along with the movement of skin tissues, contribute to the somatosensory perception of phantom movement (Reilly et al. 2006). However, only a limited number of studies on phantom mobility have investigated or even recorded these activities. This paucity of research may be due to the peripheral nervous system often being overlooked in fundamental research, which typically focuses on brain investigations. In spite of less extensive investigation, reorganization has been observed in the peripheral nervous system following deafferentation and amputation Wu; Kaas 2000. In monkeys, it has been shown that not all severed neurons degenerate; some can sprout and reach new targets. In the context of transhumeral amputation, where a limb is injured, we can hypothesize that

the sprouting motoneurons retarget injured muscle fibers and skin tissues that were previously denervated due to the amputation surgery.

In most studies, muscle activities were recorded with a single pair of sEMG electrodes placed on one head of the biceps and triceps muscles (Gagne et al. 2009; Reilly et al. 2006). This limited spatial resolution was sufficient to show that muscle activity patterns varied with the type of phantom movement (hand, wrist, or elbow) but prevented the investigation of the origin of these activities. More recent studies from our team, that used a much higher spatial resolution, have classified EMG patterns for up to eight different types of phantom hand movements (Jarrasse et al. 2017a; Jarrasse et al. 2017b), thus being able to decipher between types of phantom hand movements that are close in terms of extrinsic muscles involved (i.e. in the arm and forearm), such as flexion of the index finger and flexion of the neighbouring middle finger. These studies demonstrated that signals from several pairs of electrodes placed *on the same residual upper arm muscle* could provide relevant information about de type of executed phantom movement. Nevertheless, the underlying neurophysiological origin remains poorly understood due to the ambiguity surrounding information on which classifiers base their classification. Therefore, in this chapter, we adopted a neurophysiological perspective in the analysis of muscle activity patterns associated with phantom mobility in transhumeral amputees, in order to characterize their nature.

It was proposed that muscle activities in the residual upper arm during PHM could be new emerging activity due to reorganization of the nervous system at different levels after amputation (Gagné et al. 2011). Yet, it is also possible that such muscle contractions only reflect persisting synergistic activity originally associated with contractions of the -now missing- limb muscles. For example, synergistic activity are reported in the deltoïd and in bi-articular biceps and triceps muscle groups for stabilizing the upper limb at the shoulder and elbow joints during intact hand movements (IHM) (McKiernan et al. 1998). If such synergistic activity indeed persists after amputation,

muscle activity in the residual upper arm of transhumeral amputees during PHM should be similar to the one observed during IHM in the intact upper arm, which would give information about the origin of these muscle activities. Therefore, to better characterise the nature of the muscle activity patterns associated with PHM, we compared those occurring during PHM with those occurring during IHM. We chose not to analyze IHM of the amputees' contralateral intact arm because the compensatory use of the residual limb in daily life might influence intact arm muscle control (Garbarini et al. 2018; Makin et al. 2013). Instead, we used a control group of non-amputated participants and explored the difference between muscle activities in the intact upper arm during IHM of a single amputee and those recorded in the control participants.

II.2. Methods

II.2.1. Participants

Six participants (one female, five males) with a traumatic unilateral transhumeral amputation (P1 to P6, 24 to 75 years old) and seven controls (C1 to C7, aged 24-55 years) were included in the study. To be included, amputees had to have phantom mobility and be able to mimic their PHM with their intact hand in real time. Amputees who experienced phantom limb pain while performing PHM were excluded due to ethical reasons and because it limits their ability to move the phantom limb (Gagne et al. 2009). The delay since amputation varied from 2 to 48 years. Five of the six amputees used a myoelectric prosthesis daily. Their control relies on the generation of muscle activity in the residual triceps and/or biceps, allowing the EMG signal recorded by the two electrodes placed inside the prosthetic cuff to detect when a certain threshold is reached. The contraction of one muscle is needed to initiate a movement in one direction or the other, while the co-contraction of both muscles

Demographic data concerning the six amputated participants.

	Sex	Age (years)	Delay since amputation (years)	Amputated side	Pain treatment	Myoelectric prosthesis	Mobilization capacity
P1	F	75	14	Right	No	Yes	F1, F2, F345, Hand, Pinch
P2	M	42	5	Right	Yes	Yes	F1, Hand, Pinch
P3	M	73	48	Left	No	Yes	Hand
P4	M	49	3	Left	Yes	No	F1, F345, F2, Hand
P5	M	24	2	Left	Yes	Yes	F1, F5, Pinch,Hand
P6	M	32	4	Right	Yes	Yes	F5, Hand, F2, F1, F3, Pinch

Table II.1.: M=male; F=female. Fn= finger flexion/extension with n going from 1 (thumb) to 5 (little finger); F345=simultaneous flexion/extension of F3, F4 and F5; Pinch=thumb/index opposition opening/closure; Hand=whole hand opening/closure. The different types of PHM are indicated in the order of execution during the recording session. This order was defined according to the self-reported difficulty of movement execution, starting with the easiest.

is required to switch the mode from hand closure/opening to wrist rotation, and vice versa. P5 was the only one to own a poly-digital prosthesis but its control was similarly sequential: modifications of finger movement configurations were obtained by successive co-contractions of the two muscles. Demographic data of the amputees are summarized in Table II.1.

All amputees were recruited at IRR (Nancy, France). The control participants were recruited from the research institute (Marseille, France). The experiments were carried out in accordance with the Declaration of Helsinki of the World medical association. Written informed consent was obtained from all participants and the study received approval from a Research Ethics Committee (CERES n° 2016-57).

II.2.2. Protocol

To determine the self-evaluated difficulty in executing each type of PHM, the recording session began with a short questioning based on the detailed semi-directed interview that had been conducted previously for each participant. Amputees were instructed to execute a series of ten repetitions of a complete cycle of phantom movement (i.e., flexion/extension or closing/opening) at a self-chosen comfortable speed. They were also instructed to simultaneously mimic, symmetrically, and as accurately as possible, the movement amplitude and velocity with their intact contralateral hand equipped with a Cyberglove®II (see https://www.cyberglovesystems.com/cyberglove-ii) that recorded the kinematic data. This technique is widely used in the literature (De Graaf et al. 2016; Gagne et al. 2009; Reilly et al. 2006; Touillet et al. 2018). Movement execution began after the experimenter provided instructions on the type of movement to perform. Due to tremor or blocking (reported in the literature as an "impossibility to move despite strong effort" (De Graaf et al., 2016)) related to fatigue, for some phantom movements, the participants had to take breaks and temporally perform a different type of phantom movement before returning to the original one in order to complete the required number of 10 repetitions. Table II.1 summarizes the different types of PHM each participant executed. We paid careful attention to preserve participants from fatigue by adjusting the duration of resting periods between series of movements to their needs. In addition, each recording session was videotaped for more accurate offline visual monitoring of tremor during phantom movement execution. If this occurred, the corresponding cycle of movement was rejected from analysis. The whole recording session lasted for about 90 minutes and took place in the presence of a medical doctor.

The control group performed series of ten repetitions of the following cyclic movements with their dominant hand: flexion/extension of each of three individual fingers

(thumb, index, and middle finger), and closing/opening of hand and pinch. In an attempt to closely match these IHM with the PHM of the amputated participants, the protocol included three distinctive features. First, the IHM were executed while keeping the upper arm and forearm in a relaxed vertical position (aligned with the trunk) to match the relaxed position of the residual upper arm of the amputees. Second, control participants were asked to perform movements at a slow speed to match the average speed of the PHM performed by the amputee group (6 seconds per cycle). This was trained beforehand, and the experimenters visually verified that the speed was maintained along the session. Finally, to rule out any potential influence of intact hand mimicking on the results of the comparison between controls and amputees, the control group was also asked to accurately mimic the amplitude and speed of the IHM with their contralateral hand in real time. Kinematics was also recorded via the Cyberglove®II the mimicking contralateral hand was equipped with. Thus, measurement procedures were identical for both groups: EMG activity was recorded on one upper arm while kinematics was measured on the mimicking contralateral hand.

II.2.3. Recordings

Pairs of surface EMG electrodes were placed at various sites on the residual limb, with the placement individualized for each amputee based on the detection of muscle contractions through palpation during various types of PHM. Electrodes were placed at each location where palpation could detect a contraction for at least one type of movement, within the constraints of available electrodes. Figure II.1 shows photos with different views of the electrode locations. The present analysis focused on surface EMG signals recorded from 8 to 15 pairs of electrodes (depending on the length of the residual limb) placed distal to the deltoid muscles, i.e., only on the biceps and

triceps brachialis muscles. For one amputee participant (P6), eight pairs of electrodes were also placed on similar locations on the biceps and triceps brachialis muscles of the contralateral intact arm. For the control group, a total of 11 pairs of EMG electrodes were used for the analyses. It was not possible to precisely match the location of the electrodes on the right arm of controls to the one on the residual arm of amputees, primarily because the amputation has changed the anatomy of the upper arm muscles. Yet, we chose recording sites closely resembling those on the residual muscles of amputees (see the right side of Figure II.1). Thus, for each control participant, four pairs of electrodes were placed on the biceps brachialis (BB) and four on the triceps brachialis (TB) of the right arm. For each of these muscle groups, one pair of electrodes was placed following the SENIAM recommendations (Hermens et al. 2000), a second pair was placed distal to the first one. Finally, the two other pairs were placed laterally to the previous two pairs but still on the same muscle. The three remaining pairs of electrodes were placed, respectively, on the superficial extensor and flexor muscles of the fingers (on the forearm) and on one intrinsic hand muscle (opponens pollicis, OP) following the SENIAM recommendations. An ANT-Neuro®eego-sports system with shielded cables was used to record EMG activity at a sample frequency of 1 kHz continuously throughout the experimental session. A Cyberglove®II recorded the angular positions of the five fingers of the contralateral hand during real-time mimicking at a sample frequency of 100 Hz. Details about the calibration of the Cyberglove®II have been reported in the literature (De Graaf et al. 2016; Jarrasse et al. 2017b). Kinematic data and EMG data could be synchronized thanks to a dedicated push button which sent a marker to both recording systems at the start of each sequence of movement cycles.

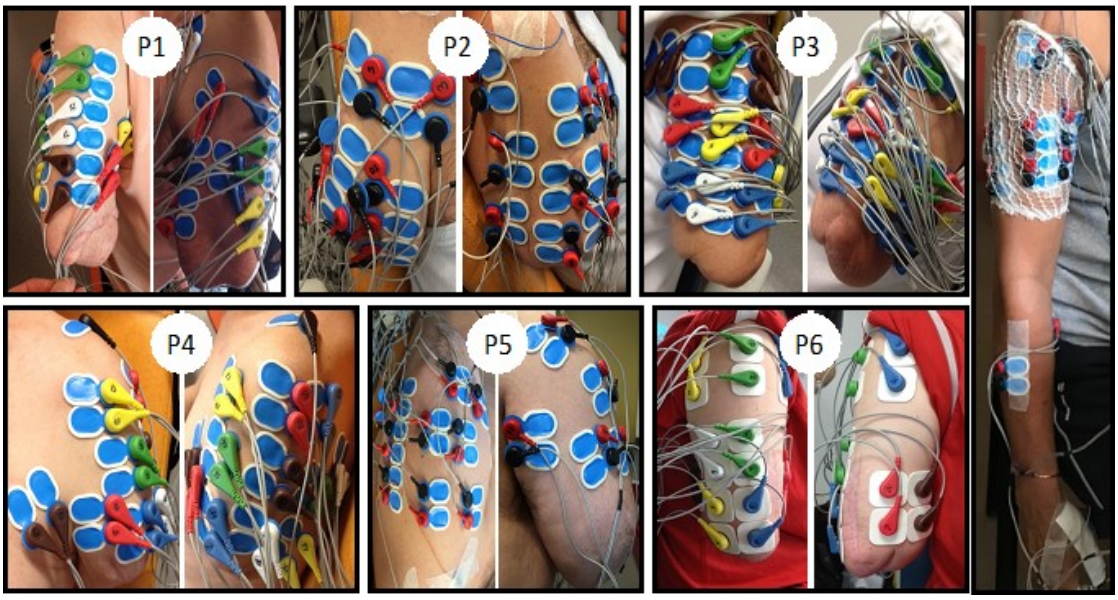

Figure II.1.: **EMG electrode placements on the residual upper arm for the six amputees (P1 to P6) and one control participant (right side).** Only the electrodes placed on the biceps and triceps were selected for further analyses. Note the non-conventional placement of 4 pairs of electrodes on the biceps muscle of the control participant. The same was done on the triceps. Participants provided their informed consent to the publication of these images.

II.2.4. Analyses

Before going into details, two methodological issues must be mentioned. First, we did not assess PHM kinematics as such (i.e. amplitude, velocity), which has already been investigated in the literature (De Graaf et al. 2016). PHM kinematics were recorded only for the purpose of analysing muscle activity patterns of each individual type of half-cycle (i.e. type of movement). Since in intact hand movements, agonist and antagonist muscle activities evidently differ in opposite movements (i.e., flexion versus extension of individual fingers, opening versus closing of pinch and hand), PHM needed to be analysed in this way as well. Secondly, as the precise placement of EMG electrodes could not be standardised across participants (both within and between groups), we devised meaningful meta-variables that were independent of the exact electrode locations. This independence was essential for enabling group comparisons,

allowing data averaging across participants within each group before comparing the two groups.

II.2.4.1. Preprocessing

Data collected with the Cyberglove®II was filtered with a 4th order Butterworth low-pass filter (cut-off frequency 2.5 Hz) and resampled at 1 kHz to match the EMG signal (see the upper trace in Figure II.2A). The EMG signal was filtered using a 4th order Butterworth band-pass filter (10-400 Hz) and series of cyclic movements were separated. EMG envelopes were calculated via the root mean square of the EMG signal over a sliding time window of 0.5 s with 0.01 increments (Jarrasse et al. 2018; Jarrasse et al. 2017b). Next, for each series of cyclic movements, we extracted the timing of phase changes from the kinematics, which were then utilized to cut the EMG activity into half cycles. Given the highly variable duration of each half cycle across different types of PHM and among participants, each half cycle repetition was normalized to a time-base representing 50% of the entire corresponding cycle. This step was necessary to later average the EMG envelopes over all repetitions for each given type of half cycle, which we will be referred to as "movement type" (e.g., thumb flexion, thumb extension, whole hand opening). The EMG envelopes are shown in Figure II.2B. All kinematic and EMG analyses were done with the help of a custom-made MATLAB (version 2018b) script.

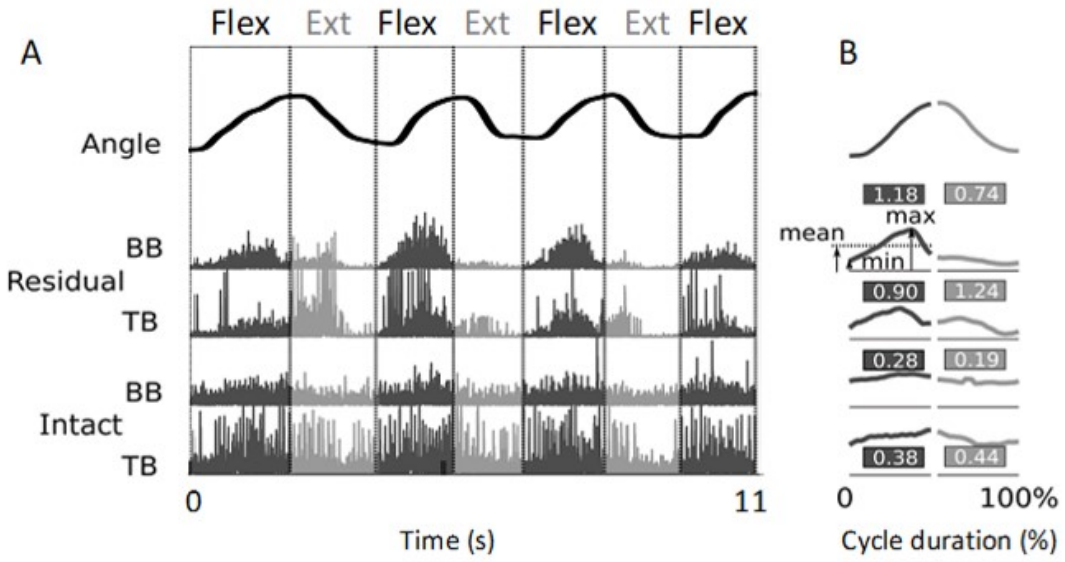

Figure II.2.: **Illustration of EMG signal processing resulting in relative phasic muscle activity values.** (A) The top trace shows the angular evolution of 3.5 cycles of flexion/extension of the little finger executed over 11 s. The four lower traces represent the corresponding rectified EMG activity normalized, for each electrode site, by the maximum value, recorded from the biceps (BB) and triceps (TB) brachialis muscles of the residual arm and intact upper arm respectively. (B) Mean kinematic traces and EMG envelopes for each half cycle. The duration of each movement half-cycle is normalized to 50% of the total cycle time. The values indicate the relative phasic muscle activity calculated from the signals shown in A (see text). Note the higher values found for the residual upper arm compared to the intact upper arm.

II.2.4.2. Relative phasic muscle activity

Figure II.2A shows typical examples of rectified EMG recordings. These recordings were obtained from two sites, one on the residual and one on the intact upper arm of participant P6 during flexion/extension of the phantom and intact little finger, respectively. During the PHM, clear phasic muscle activity was recorded from the biceps and triceps brachialis of the residual upper arm, whereas during the IHM, the intact upper arm showed mainly tonic muscle activity. Since the required task was to perform cyclic hand and finger movements and not to maintain postures, we developed a method to better distinguish phasic from tonic EMG activity. This

was also used to normalize the amplitude of the recorded EMG signals instead of using the classical normalization to the maximal voluntary contraction, which was not applicable. Thus, in this cyclic action, the relative phasic muscle activity was quantified as follows: for each half cycle and recording site, the difference between the maximum and minimum values of the averaged envelope was divided by its mean value. For each participant, each pair of electrodes and each type of phantom or intact hand movement, the mean relative phasic activity over the ten repetitions was quantified. The obtained value was higher in case of purely phasic activity and lower when the bursts were superimposed on a tonic background (see Figure II.2B for an illustration). For each participant, this value was averaged across all movement types and electrode sites to make inter- and intra-group comparisons of the relative phasic muscle activity between (i) the residual and intact upper arm, (ii) the residual upper arm and intact forearm, (iii) the intact upper arm and forearm.

II.2.4.3. Movement-type and electrode-site specificities

In order to study the specificities of activity patterns in the residual upper arm muscles during PHM and compare these to muscle activity patterns in the intact upper arm during IHM, we developed 2 meta-variables: movement-type specificity and electrode-site specificity. First, the variation in relative phasic muscle activity across different movement types for a given pair of electrodes indicates whether this site is specifically activated for certain types of movements. We will refer to this as "*movement-type specificity*" and quantify it for each electrode site as the standard deviation of the relative phasic muscle activity values across different movement types (SD_m). A high SDm value indicates that this site is movement specific (see Figure II.3A and II.3C at each electrode site). Conversely, a low SDm value indicates that the relative phasic muscle activity is similar across different types of movements at that site, indicating a lack of movement specificity (see Figure II.3B at each electrode site). Secondly, the

variation in relative phasic muscle activity across different electrode sites for a given type of movement reflects the specific involvement of certain muscle volumes located under these electrodes for this type of movement. We will refer to this as "*electrode-site specificity*" and quantify it for each type of movement as the standard deviation of the relative phasic muscle activity values across electrode sites (SD_e, low in Figure II.3A vs. high in Figure II.3B and C). For each participant and arm segment (either forearm or upper arm), the "*global movement-type specificity*" (*SDM*) was calculated by averaging the SDm values across all electrode sites. For a given participant, a high SDM value indicates a high movement-type specificity at many electrode sites (as in Figure II.3A and II.3C). Yet, this quantification does not exclude that all electrodes may record the same relative phasic activity for a given type of movement (as in Figure II.3A). Therefore, we also determined the "*global electrode-site specificity*" (*SDE*) by averaging the SD_e values over all movement types. To perform inter-group comparisons, values of *global movement-type* and *electrode-site specificities* (i.e., SDM and SDE) of all participants were grouped and compared between PHM and IHM.

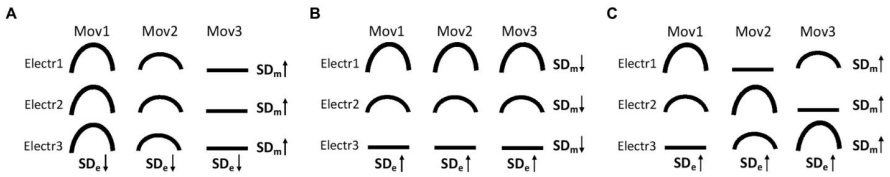

Figure II.3.: **Three examples of schematic movement type (SD_m), electrode site (SD_e) and global (SDE and SDM) specificities (A,B,C).** ↑ and ↓ reflect, respectively, "high" and "low" specificities. A: low SDE and high SDM, B: high SDE and low SDM, C: high SDM and high SDE.

II.2.4.4. Statistics

Because of the non-normal distribution of data, probably due to the restricted sample size related to the restricted population of transhumeral amputees, two-tailed comparisons between PHM and IHM were statistically tested using the non-parametric

Wilcoxon Rank Sum test (independent samples, n=6 for the amputees; n=7 for the control group). The Wilcoxon Signed Rank test was used for the two-tailed *paired* comparison of relative phasic activity between the forearm and upper arm in control participants (n=7). Statistical testing was performed in R-4.3.2 with the significance threshold set at 0.05, except for the 2 comparisons concerning the Relative phasic activity of the residual arm where a Bonferroni correction lowered it at 0.025. The values of test statistics, the p-values and the confidence intervals of the estimator (i.e. the pseudo-median, see Hollander et al. 2014) were all given by R.

II.3. Results

PHM was associated with reproducible phasic muscle activity that varied with movement type and electrode site. Figure II.4A displays typical examples of EMG signals from participant P6 for 3 consecutive repetitions of various types of PHM, recorded from four pairs of electrodes on the residual upper arm. First, it can be observed that EMG activity is phasic and that for a given type of PHM, it is repeatable. These phasic activities are coherent with the kinematics of movement: the EMG bursts show an increasing amplitude at the start of a movement and decreasing amplitude at the end, irrespective of the half-cycle duration (see Figure II.2A for illustration). As expected from a muscle directly involved in IHM, similar observations are noted regarding the signals recorded from the forearm superficial finger flexor muscle. Second, for each electrode site, the EMG activity varies according to the type of PHM. Distally on the lateral head of TB (3rd trace), activity was higher for isolated extensions of the thumb and index finger (F1Ext and F2Ext) than for their flexions (F1Flex and F2Flex) but inversely lower when involved in hand opening and closing. Such intra-individual variability has also been observed for the other amputated participants. Finally, as expected from a fusiform muscle such as TB, EMG recordings on a proximal and a

more distal site (two top traces for Figure II.4A) present similar movement-dependant activities. In Figure II.4B, signals were recorded from the intact upper arm muscles and the superficial finger flexor muscle of a control participant executing different types of IHM. As expected from a forearm muscle directly involved in hand movement, the superficial finger flexor muscle exhibited EMG bursts (i.e. phasic activity) for the different types of movements. Interestingly, this activity seemed very similar to the phasic EMG activity measured on the residual upper arm during such movements. In contrast, all sites on TB and BB exhibited mainly tonic activity.

PHM was associated with relative phasic muscle activity on the residual arm, which was stronger than that associated with IHM in the upper arm and similar to that associated with IHM in the forearm. As could be expected given the EMG traces shown in Figure II.4 for individual participants, 'relative phasic muscle activity' associated with PHM recorded on the residual limb was found to be significantly higher than that associated with IHM recorded on the intact upper arm (W=42, p≈0.003, Table II.2a) (Figure II.5). Furthermore, relative phasic muscle activity associated with IHM measured on the intact forearm muscles was significantly greater than that measured in parallel on the intact upper arm (V=28, p≈0.02, Table II.2b). The low values for the intact upper arm muscles are typical of the tonic EMG activity depicted in Figure II.2A and Figure II.4. We found no significant difference between PHM-related relative phasic muscle activity and IHM-related relative phasic muscle activity measured on the forearm of control participants (W = 35, p≈0.051, Table II.2c). Finally, in participant P6 of the amputee group, EMG signals were not only recorded from the residual upper arm but also simultaneously from the intact upper arm during PHM. In Figure II.5, results corresponding to P6 are represented by the two circles connected by a line. The difference in relative phasic muscle activity between the residual upper arm during PHM and the intact upper arm during the IHM mimicking the PHM, is consistent with findings from the group comparison.

The relative phasic muscle activity on the upper arm varies more with both the type of movement and the recorded site when associated with PHM than when associated with IHM. We compared movement-type and electrode-site specificities between PHM and IHM in the signals recorded from the upper arm muscles (Figure II.6). Both for movement type (W=42, p≈0.003, Table II.2d) and electrode site (W=39.5, p≈0.01, Table II.2e), the results show that EMG patterns associated to PHM and measured on the residual arm were more specific than EMG patterns associated to IHM and measured on the intact upper arm of control participants. This demonstrates that any muscle activity on the residual upper arm during PHM is more directly related to the type of movement and the precise position of the electrode, even within a given muscle, than is the case for the intact upper arm during IHM.

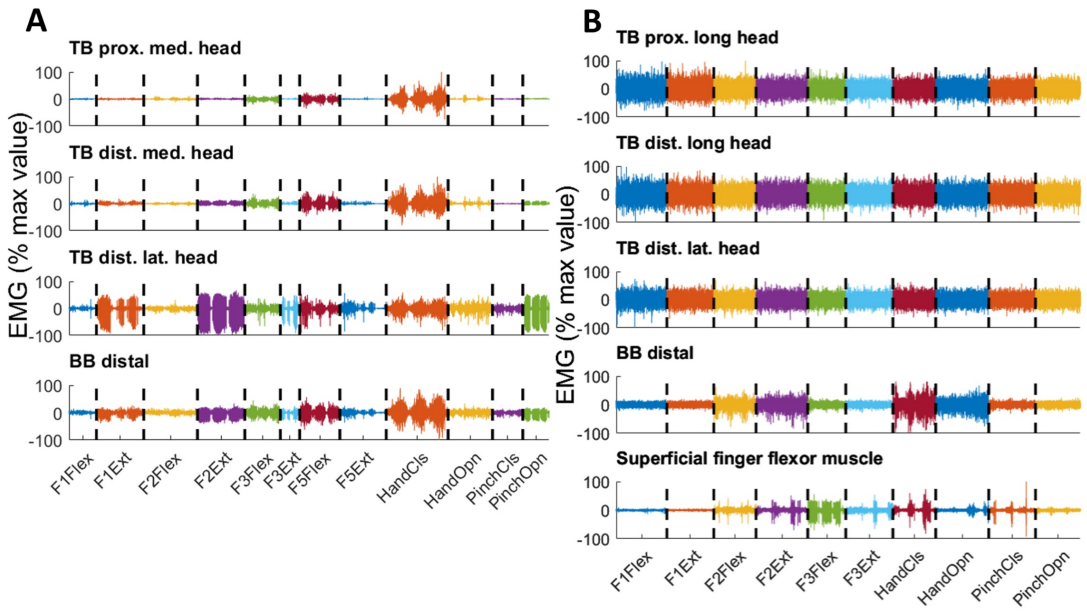

Figure II.4.: Three consecutive repetitions per type of movement are displayed, distinguished by color for selected pairs of electrodes recorded in parallel on the residual arm of participant P6 (A) and the intact arm of a control participant (B). Both PHM-related and IHM-related EMG signals were concatenated over different types of movements. The different types of movements are flexion (Flex) and extension (Ext) of thumb (F1), index (F2), middle finger (F3) and little finger (F5), closing (Cls) and opening (Opn) of hand and pinch. For each pair of electrodes, the signal is normalized by the maximum peak EMG amplitude found over all movement types and expressed in percentage. (A) Upper trace: proximal location on the medial head of triceps brachialis (TB); second trace: distal location on the medial head of TB; third trace: distal location on the lateral head of TB; lowest trace: distal location on BB. (B) Upper trace: proximal location on the medial head of biceps brachialis (BB); second trace: distal location on the medial head of BB; third trace: distal location on the lateral head of BB; lowest trace: superficial finger flexor muscle. Note that the lack of phasic activity in the intact arm muscles resulted in high normalized values, misleadingly suggesting high EMG levels.

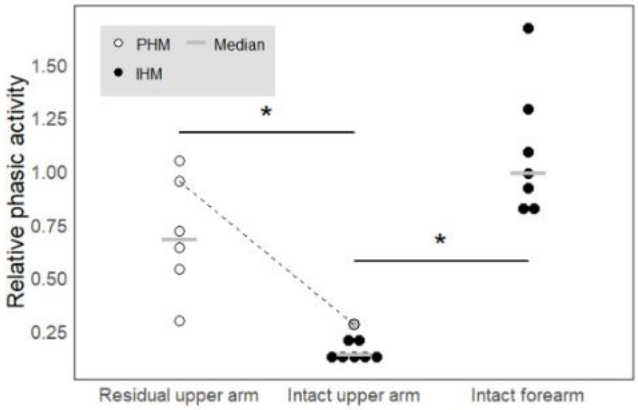

Figure II.5.: Relative phasic activity across movement types and electrode sites. A high value indicates a phasic profile while a low value indicated a rather tonic profile. In each condition, each circle represents one participant. White circles correspond to amputees while black filled circles correspond to controls. The grey circle added to the intact arm category corresponds to the results obtained for amputee P6 for whom we recorded the residual and intact upper arms in parallel. The dotted line links the data obtained for P6 in the two conditions. The grey horizontal lines represent median values. * indicates significant differences ($p<0.05$). See text for precise p-values.

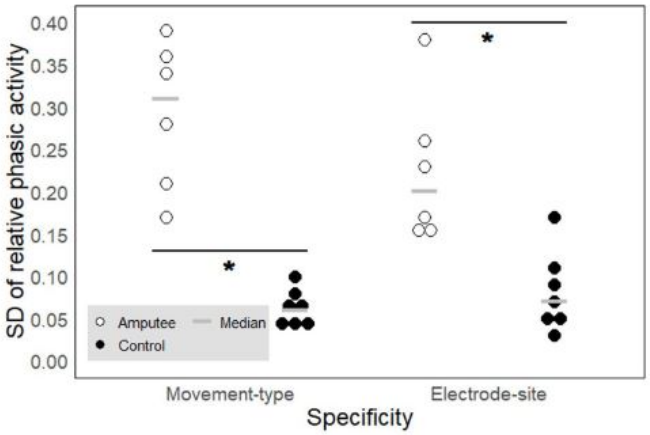

Figure II.6.: Movement-type and electrode-site specificity of the patterns of phasic activity. Each circle represents one participant. The signals were measured on the upper arm for phantom (PHM, amputees, empty circles) and intact (IHM, controls, filled circles) hand movements and expressed in SD of the relative phasic muscle activity. A high SD value reflects a high specificity. The grey horizontal lines represent median values. * indicates significant differences between the two groups (see results section for precise p-values).

Statistical analyses to compare muscle activity patterns during IHM and PHM using the relative phasic activity and its variability across movement-type and electrode-site..

Comparison	Data Structure	Type of test	Power
a Relative phasic activity residual *VS* intact upper arm	Non normal	Wilcoxon Rank Sum test (unpaired samples)	W=42 p ≈ 0.003 95% CI: [0.19; 0.84]
b Relative phasic activity intact forearm *VS* intact upper arm	Non normal	Wilcoxon *Signed* Rank test (paired samples)	V = 28 p ≈ 0.02 95% CI: [0.66; 1.25]
c Relative phasic activity intact forearm *VS* residual upper arm	Non normal	Wilcoxon Rank Sum test (unpaired samples)	W = 35 p ≈ 0.051 95% CI: [-0.03; 0.75]
d Movement-type specificity	Non normal	Wilcoxon Rank Sum test (unpaired samples)	W = 42 p ≈ 0.003 95% CI: [0.13; 0.32]
e Electrode-site specificity	Non normal	Wilcoxon Rank Sum test (unpaired samples)	W = 39.5 p ≈ 0.01 95% CI: [0.06; 0.23]

Table II.2.: W, test statistic value for Wilcoxon Rank Sum test; V, test statistic value for Wilcoxon Signed Rank test.

II.4. Discussion

By adopting a neurophysiological perspective in the analysis of activity patterns in the residual upper arm associated with phantom mobility in transhumeral amputees, the first aim of this study was to characterize their nature. For this, we compared the muscle activity patterns on the residual arm during PHM with those during similar IHM on the intact arm of controls. The meta-variables were chosen in order not to base the analyses on comparisons of specific electrode sites between controls and amputees. Instead, we computed the relative phasic muscle activity and its variability across movement types and electrode sites for each participant, that we then compared between groups of participants. This permitted to overcome the unavoidable variability in electrode placements across participants induced by heterogeneity factors such as the anatomy of the upper arm muscles that changes after amputation and as a function of the length of the residual limb.

Our results show significant differences in upper arm muscle activities between IHM and PHM. Muscle activity in the upper am during IHM was characterized by highly tonic signals and uniform patterns depicted through low movement-type and low electrode-site specificities. On the other hand, during PHM, the residual upper arm muscle activity appeared to be phasic and highly correlated with the kinematics of the movement, irrespective of the duration of the movement half-cycle. When quantified, this PHM-related activity exhibits significantly higher relative phasic activity as well as both movement-type and electrode-site specificities. Moreover, the relative phasic activity values were comparable with those seen in the forearm and intrinsic hand muscles during IHM. In the intact upper arm, while the low electrode-site specificity can be explained by the wide distribution of the muscle fibers of each individual motor unit throughout the entire muscle, allowing for homogeneous muscle contraction,

the low movement-type specificity is consistent with the expectation that separate movements of intact adjacent fingers are associated with tonic activity patterns in the upper arm, allowing to stabilize the more proximal joints. If the activity in the residual upper arm muscles during PHM had remained with the same tonic synergistic activity as the one before amputation during IHM, one should have found similar results. However, as this is not the case, our results do not support residual synergistic activity as being the sole reason for the existence of phasic muscle activities and localized muscle contractions in the residual upper arm during PHM, but rather suggest neural reorganization.

The general consensus states that upper limb amputation leads to reorganization at the cortical level, where the deafferented area in M1 and S1 would be invaded by the neighbouring areas (i.e., residual limb and face) erasing the functional representation of the lost limb (Ojemann; Silbergeld 1995; Lotze et al. 2001; Navarro et al. 2007). These intraoperative studies of cortical mapping were completed by more recent studies using transcranial magnetic stimulation (TMS). Applying TMS over the area of M1 that controlled the hand before amputation, resulted in muscle contractions in the residual upper arm (Gagné et al. 2011) while evoking a sensation of movement in the phantom hand (Mercier et al. 2006). These two latter studies used only one pair of EMG electrodes on each muscle of the residual limb, consequently failing to unveil the electrode-site specificity discovered in the present study. However, exclusive central reorganization cannot explain the high electrode-site specificity of the patterns observed in our study. Instead, our findings suggest that specific sub-volumes within upper arm muscles are selectively activated during phantom hand movements (PHM). This hypothesis finds support in research on both human and non-human primates. First, during phantom hand movements, activity in the severed peripheral median and ulnar nerves have been measured in severed nerves of human amputees

(Dhillon et al. 2005; Jia et al. 2007). Second, surgical muscle reinnervation targeting specific nerve fascicles enables independent control of focal muscle compartments (Bergmeister et al. 2017; Woo et al. 2016). Finally, natural peripheral neuromuscular reorganization, observed in monkeys after transhumeral amputation, involved axonal sprouting of severed motoneurons that controlled hand muscles before amputation and recapture of surrounding denervated muscle fibers in the residual upper arm, forming new neuromuscular junctions (Qi et al. 2004; Wu; Kaas 2000). It is worth noting that due to relatively distal localization of motor endplates in the upper arm muscles (1/3 of the upper arm length above the elbow joint, Guzmán et al. 2011), many muscle fibers are likely left without innervation after transhumeral amputation, increasing the likelihood of their capturing by severed spinal motoneurons. Consequently, cortical motoneurons initially controlling hand muscles would eventually govern muscle volumes in the residual limb. While the connection between natural sprouting- and recapture-mediated peripheral reorganization and phantom mobility hasn't been explicitly established, the present study, and precisely the specific and focal activity patterns observed in the residual upper arm muscles during phantom limb movement execution, aligns with such reorganization. However, further research is required to confirm this hypothesis.

Our study may contain potentially limiting methodological issues that should be discussed.

Mimicking with the intact hand. This method is often used in the literature since it is the only way to objectively determine the timing of phase changes in order to cut the EMG activity into half cycles. Yet, one might raise the question whether synchronous mimicking could have influenced the EMG patterns on the residual limb. This seems not to be the case, as shown, for instance, by Jarrassé and collegues in their EMG-pattern classification study (Jarrasse et al. 2017b). In order to correctly identify

phantom movement types, they used mimicking during the *learning* *phase* of the classifier but not during testing, and the high success rate of the classifier in correctly recognizing the executed movement types showed that mimicking with the intact hand did not influence the EMG patterns associated with phantom hand movements.

Suitability of the electrode sites. Electrode placement can affect the content and quality of EMG signals. It is precisely for this reason that we used an 'unusual' electrode placement on the intact arm to record adjacent volumes on the same muscle, resembling the electrode sites on the residual arm of amputees. Yet, we did not observe identical results, particularly with regard to the electrode specificity of the EMG patterns. The poorly specific EMG profiles found on the intact arm were expected in the biceps and triceps muscles due to their tonic type activities during finger and hand movements. Despite the similar placements of electrodes on the residual arm, EMG variability across recording sites is much higher. One might still raise the question whether we may have missed information, in particular because we did not cover the entire surface of the residual limb. Yet, we used 8-15 pairs of electrodes (depending on the length of the residual limb), carefully placed using palpation. Jarrassé and colleagues, using the same method, showed that this was sufficient to classify 8 different phantom movements with a success rate of over 85% (Jarrasse et al. 2018). Therefore, we believe that in the present study, most relevant information was captured.

Choice of the control condition. In the introduction section, we mentioned the potential risks associated with selecting the contralateral arm of amputated participants as the control condition. In order to avoid biases in our results, comparison between PHM and an intact residual limb movement involving the biceps and triceps would have been optimal. However, residual limb movements concern the shoulder articulation (ante/retropulsion and adduction) for which the deltoid muscle alone usually is sufficient, especially after transhumeral amputation. Finally, while comparing muscle activity patterns during PHM to those during phantom elbow movements may seem

plausible, it is also not ideal for two reasons. First, phantom segments and joints as well as their mobility are mostly present at the most distal segments of the upper limb (Touillet et al. 2018, study on 76 amputees). Thus, most amputees cannot perform phantom elbow movements for the simple reason that they either do not feel the phantom elbow or cannot move it. Among our 6 participants, only 2 perceived their phantom elbow (P4 and P5) and only 1 of them could execute elbow flexions and extensions (P5). When an amputee is asked to perform a phantom movement at a joint that they do not feel or cannot move, either there is no EMG signal (Reilly et al. 2006) or this leads to major coactivation of the residual limb muscles as the participant attempts to perform this impossible task. Second, even when the phantom elbow is present and can be moved, the residual limb muscles acting on the elbow joint are not activated in the same way as before amputation, as transhumeral amputation severed these muscles and expectedly removed many of their motor endplates. Therefore, capturing of denervated muscle fibres by severed spinal motoneuron sprouting (whether originally projecting on hand, forearm or the same upper arm muscles) can be expected. All these reasons make the use of phantom elbow flexions as a control condition very doubtful. We therefore believe IHM of control participants to be the most reasonable control condition for comparing patterns of muscle activity on upper arms.

Limited number of participants. The limited sample size in terms of participants in research focusing on specific populations is a well-known problem, in particular the recruitment of participants satisfying our inclusion criteria and willing to give half a day of their time. Although a larger population would have been preferable, other studies concerned similar number of participants (Gagne et al. 2009; Jarrasse et al. 2018; Jarrasse et al. 2017a; Reilly et al. 2006; Touillet et al. 2018). If we had not found a significant result in the present study, this limited number of participants would have been a matter of great concern. However, despite differences across participants in

delay since amputation, level of upper arm amputation, pain treatment, and age, all 6 participants showed much greater EMG variability across electrode localisations and movement types during phantom hand movement execution compared to intact hand movements in non-amputated control participants. Concerning pain treatment, although this might reduce the intensity of phantom sensations (or even sensations in general), it seems not to influence the capacity of producing phantom movements, as shown in the epidemiological study of Touillet and colleagues (Touillet et al. 2018). Finally, regarding the influence of age on neuromuscular mechanisms, two of our participants were older than 70 years which means that they might have been affected by the age-related phenomenon of denervation/reinnervation. This phenomenon involves muscle fibres that were once part of fast motor units being reinnervated by the motoneuron of a slow motor unit, eventually leading to an increase in the size of the latter (Piasecki et al. 2016). This mechanism ultimately increases the mean size of motor units, which explains the decline in motor control precision with age. However, we observed the opposite in the present study: contrary to intact upper arm muscles, smaller muscular volumes contract differently for different types of phantom hand movements, which strongly suggests a reduction in the size of motor units. We therefore believe that the observed phenomenon in the present study is as robust as those previously published on phantom mobility.

Limited number of trials. The limited sample size (10 repetitions per type of movement) was a necessity. Indeed, untrained phantom movements are slow (performing a cycle of finger flexion/extension or hand opening/closing takes on average 6 seconds and can sometimes take more than 30 seconds). They are reported to be exhausting (De Graaf et al. 2016), and the required 10 repetitions are sometimes impossible to perform consecutively because they are too strenuous. On the other hand, in the absence of signs of fatigue, EMG patterns show remarkable reproducibility across movement cycles even when not performed consecutively and 10 repetitions are suffi-

cient to allow classification of these patterns and thus define the movement performed as distinct from the others (Jarrasse et al. 2017a; Jarrasse et al. 2017b). To maintain the reproducibility of the EMG patterns and thus limit the effects of fatigue on the recorded EMG patterns, if we observed any signs of visible fatigue such as slower movements, slight tremors or freezing (i.e., the hand feels as clamped in a vice and cannot be moved), we halted the recording and provided the participants with a short break. To limit fatigue even further after the break, we suggested that participants perform another type of phantom movement instead of directly resuming the original 10-cycle series. Due to the necessary precautions taken, the recording of all potential phantom movements required at least 1.5 hours for each participant. Requesting additional recordings seemed likely to induce fatigue.

Randomization of trials. Our experimental design would be insufficient in a study on intact participants, but in the case of phantom movements in untrained amputees, similar randomization is more difficult to implement. Indeed, our participants needed intense concentration because none of them were used to producing phantom movements. Thus, if we had to randomize our 10 repetitions without increasing the number of trials, we would need additional periods of concentration between each movement execution, which would inevitably lengthen an already long experimental session and potentially induce fatigue that we were in fact trying to avoid. Jarrassé and colleagues used EMG activity associated with phantom hand movements in transhumeral amputees and to test whether the observed muscle activity patterns on the residual upper arm were classifiable (and thus reproduceable) as a function of the executed type of movement (Jarrasse et al. 2017a; Jarrasse et al. 2017b). For this, during the learning phase of the classifier, they used either 2 cycles or 10 cycles executed in a row, and then tested the classifier with movements performed *one at a time* (i.e., without repetitions). The success rate of classification was about 80% when considering six different types of movement, which was similar to general classification rates in the

literature of surface EMG activity in forearm amputees who still have residual hand muscles (Cipriani et al. 2011; Smith; Hargrove 2013). This shows that the patterns of EMG activities are similar and reproducible whether the phantom movements are executed in a row or randomly, one at a time. Thus, we believe that randomisation would not have fundamentally changed the outcome of this study.

Use of prosthetic limbs. Some of our participants were using a prosthetic hand daily and it might be argued that the specificity of EMG associated with phantom hand and finger movements is correlated to the ability of the amputee to use a myoelectric hand. But phantom mobility and the control of current conventional myoelectric prostheses do not influence each other (Touillet et al. 2018). This is particularly the case of transhumeral amputees. Indeed, the control of their prosthetic hand and wrist movements is based on the production of muscle activity in the residual upper arm muscles for which the recorded EMG signal should reach a certain threshold. The signals are typically recorded by only two pairs of electrodes placed on antagonistic muscles, i.e., the biceps and triceps in transhumeral amputees. Even for the amputees who use a complex poly-digital hand prosthesis (e.g., P5), the different finger movement configurations are controlled through simple succession of basic co-contractions of the two antagonistic muscles. This control does not allow the use of the poly-digital hand prosthesis to its full potential. On the other hand, the patterns we recorded during PHM through the use of multiple electrodes are sufficiently complex to be classified as distinct patterns that are systematically associated with *specific individualized finger movements* (Jarrasse et al. 2017a; Jarrasse et al. 2017b). Therefore, in no case can the distributed muscle activity we observed be a learned feature associated with the use of their myoelectric prosthesis. Moreover, transhumeral amputees can clearly distinguish between the action required to elicit prosthetic movements and the action that provoked the natural somatosensory feedback involved in voluntary movement of the phantom hand (Touillet et al. 2018). In the former, participants concentrate on

producing a specific EMG intensity set by the system's threshold, which is challenging and must be learned (Graaf et al. 2004). It is the visual feedback of the prosthesis moving or the auditory feedback (the beep) of the system switching configuration that validates the action. In the latter case, the EMG pattern appears naturally inducing somatosensory feedback from the tissues in movement in the residual arm, thereby giving feedback on the generated movement without the need for a learning phase (De Graaf et al. 2016). All of these findings highlight the primary advantages of PHM-based myoelectric prosthesis control over conventional methods, particularly for individuals with transhumeral amputations.

In conclusion, the present study strongly suggests that the muscle activity systematically associated with phantom hand mobility could, at least partly, originate from the sprouting of axotomized spinal motor neurons and the retargeting of residual muscle fibers. Even if this sprouting has already been highlighted in monkeys, this is left to be verified in humans. One could conduct longitudinal studies using echography of the residual limb, in parallel with investigation on the mobilization capacities of the phantom limb. To advance prosthesis control, rehabilitation protocols should incorporate training for phantom mobility which increases the number of executable phantom movement types (Touillet et al. 2018) and consequently enhance the capacity of control over the phantom hand. In the following chapters we investigated the effects of training on phantom mobility. In particular, Chapter 3 investigates if machine learning classification of muscle activities in the residual limb, which could be used in prosthesis control (Jarrasse et al. 2017b; Touillet et al. 2018) is improved after phantom movement training at home.

III. Phantom movement training without classifier performance feedback improves mobilization ability while maintaining EMG pattern classification

III.1. Introduction

As mentioned in the introductory chapter, several reports (De Graaf et al. 2016; Touillet et al. 2018; Gagne et al. 2009) have indicated the difficulty of phantom movement execution and demonstrated, through the use of kinematic data, their resulting slowness compared to IHM. Yet, phantom mobility can be trained in various ways similarly to what can be done in mobility of intact limbs. Phantom movement training has mostly been investigated to treat phantom pain through virtual reality using pattern recognition (PR)[1], or mirror therapy (Ortiz-Catalan et al. 2016; De Nunzio et al. 2018).

[1] Pattern recognition operates on the premise that every motor action is associated with a consistent and identifiable muscle activity pattern, described by fundamental attributes such as amplitude and frequency. These classifiers, used in PR algorithms, require training with labeled EMG data corresponding to specific movements.

A few other studies have tried to link phantom movement training to a possible improvement in movement perception and control. Thanks to an instrumented glove that allows to collect kinematic data through mimicking of PHM with the intact hand in real time, Garbarini and colleagues showed that after a short period of phantom finger-tapping training, the execution speed was increased (Garbarini et al. 2018). While this study included only one amputee with phantom mobility, one of our team's recent studies (Touillet et al. 2018) took interest in 5 participants. These participants, who had undergone a transhumeral amputation a few years earlier, participated in a two-month protocol of daily PHM training. With training, it appeared that PHM became faster and more enduring, as shown by the increasing number of repetitions a given phantom movement was executed without blocking. Moreover, new types of PHM became achievable with training. No evolution was seen when no training was performed (Touillet et al. 2018). Overall, these results suggest that training phantom movements improves some aspects of phantom mobility in transhumeral amputees. However, no study has investigated how the improvement of such features through training could translate itself into changes in the associated muscle activity patterns. As seen in sports training, we expect to observe muscle activity correlates of the perceived improvement.

As developped in the previous chapter, muscle activity patterns in the residual upper arm during PHM, display a high spatial specificity compared to what is recorded in the upper arm during IHM. This strongly suggests a neuromuscular reorganization through sprouting and retargeting similar to the one naturally observed in monkeys (Wu; Kaas 2000) and the one orchestrated in Targeted Muscle Reinnervation (TMR; Cheesborough et al. 2015). In the former, sprouting allows severed nerves that formerly inervated muscles direcly involved in hand movement prior to amputation to retarget muscle fibers in the upper arm that had been denervated due to the amputation surgery. In the latter, surgery consists in denervating new muscle targets so that

the transferred nerves severed by former amputation can be provided with targets. The aim of this process is to improve myoelectric prosthesis control. Here we wanted to analyze muscle activity further to determine if the improvement in movement perception was reflected in muscle activities and thus motor commands through the use of various variables including some on the performance of a pattern recognition algorithm applied on these muscle activity patterns.

A few studies have focused on combining training and PR based on EMG signals. But only below-elbow amputees were included in these studies (Powell et al. 2014; Fougner et al. 2014; Nakamura et al. 2017; Anderson; Bischof 2014; Montalivet et al. 2020), never transhumeral amputees. Moreover, the types of training that were chosen required expensive laboratory set-ups, which limits the number of amputees that could benefit from it in a clinical context. Finally, the feedback provided during training was based on performance of the PR algorithm, which allowed the participants to adapt their movements to increase this performance by modifying the information contained in the EMG signals (e.g. Montalivet et al. 2020). Such training may have eventually resulted in movement intentions that did not match the prosthesis movements, making the control of movements feel unnatural and difficult to reproduce. Now, the interest of PHM is to obtain natural and intuitive control (i.e., without mismatch) which is ergonomic and contributes to the embodiment of the prothesis (e.g. Powell et al. 2014).

To avoid the previously cited disadvantages caused by feedback on PR performance, we chose to consider another type of training: a two-month daily PHM training *at home* with no other feedback than natural somatosensory information. The aim of the present study was to explore whether improvements in kinematics following home training (Touillet et al. 2018) were accompanied by an increase in PR performance. For six amputees (of whom 5 above-elbow), we compared the PHM kinematics and the muscle activity on the residual limb between before and after training. We classified

EMG patterns to evaluate the change in the amount of information usable by the classifier.

III.2. Methods

III.2.1. Participants

Six male participants (P1 to P6, 24 to 75 years old) with an amputation of their dominant upper limb were included in the study. Four of them were above-elbow amputees (P1-P4), P5 was a below-elbow amputee, and P6 had a scapulothoracic disarticulation. The inclusion criteria are the same as the ones for the first study (see Chapter II). They all declared motivation to train daily at home by repeating all the phantom movements that they could perform. Amputees who experienced phantom limb pain while performing PHM were excluded. The time since amputation varied from 1 to 34 years. Three of the 6 amputees used a myoelectric prosthesis daily, controlled by the classical threshold-based method (on/off and co-contractions strategy). The demographics of the participants are summarized in Table III.1. This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from all participants and the study received approval from the Clinical Research Ethics Committee (CERES N° 2016-57).

III.2.2. Protocol

All participants performed two recording sessions, one before and one after the two-month home training period. Each recording session started with a short questioning to determine the different types of PHM the participant could perform and the self-assessed difficulty in performing them. The tested movements were actual movements that involved a change of hand posture : individual finger movements, clos-

Demographic data concerning the six amputated participants.

	Sex	Age (years)	Delay since amputation (years)	Amputated side	Level of amputation	Myoelectric prosthesis	Mobilization capacity
P1	F	42	5	Right	TH	Yes	F1, Hand, (F1,F2,Wfl)
P2	M	49	3	Left	TH	No	F1, F345, Wfl, F2, H, Winc
P3	M	24	2	Left	TH	Yes	F2, P, H,(F1,F5)
P4	M	58	34	Left	TH	No	P,H,Wfl,Winc, (F1)
P5	M	40	1	Left	TR	Yes	F1, F5, F23, P, H, Wfl, Winc, (F3, F4)
P6	M	57	6	Right	SD	No	F1, F2, F5, F2345, H, Wfl, (F3,F4)

Table III.1.: TH=transhumeral, TR=transradial, and SD=scapulothoracic disarticulation. R=Right, L=Left. For all participants, the amputated arm was the dominant one before amputation. Fx = flexion and extension of finger x (with 1=thumb...5=little finger), Fxy =fingers x and y together, P=Pinch opening/closing, H=Hand opening/closing, Wfl=wrist flexion/extension, Winc=wrist ulnar/radial inclination. The new movements that became achievable during the training period are between brackets in the last colon.

ing/opening of the hand and pinch, and global hand movements around the wrist (flexion/extension and inclination). Movements were recorded from easiest (less effortful) to most difficult. For each movement, the participant was instructed to simultaneously mimic the kinematics of the PHM (amplitude, velocity; for more details see De Graaf et al. 2016) with his intact hand, so that EMG activity was recorded on the residual upper limb while kinematics was measured from the contralateral hand. Each type of PHM was performed in series of up to 10 repetitions of a complete cycle (i.e., flexion/extension or closing/opening) at a comfortable speed chosen by the participant himself. Special care was taken to protect participants from fatigue. If the participant could not perform 10 cycles in a row (e.g., movement blocking, residual limb tremor), the recording was stopped and the participant rested for a few minutes before recordings were resumed for either the same or another type of movement. This was repeated until a total of 10 cycles was reached for each movement type. Each session lasted approximately 60 minutes and was video recorded. Recordings took place in the presence of a medical doctor.

Between these two recording sessions, the participants were asked to find a moment each day to train their PHM. They were instructed to execute as many cycles as possible (up to 15) without blocking. If they felt that they were able to perform a new type of PHM (i.e., one they were previously unable to execute), they had to integrate this movement into their daily training. Contrary to recording sessions before and after training, the participants were specifically instructed not to mimic the PHM with their intact hand. They were also instructed to stop immediately if the training induced pain. During the training period, a weekly phone interview was organized to evaluate compliance, tolerance, and observance. Each training session was reported to take at most 15 minutes.

III.2.3. Recordings

The kinematics of the mimicked phantom finger movements were recorded on the intact hand using a Cyberglove®II, at a frequency of 100 Hz. Details on the calibration of the Cyberglove have been reported previously (Jarrasse et al. 2017a; De Graaf et al. 2016). Global hand movements around the wrist were recorded with an inertial measurement unit (IMU, nine degree-of-freedom Sensor Stick from Sparkfun ®) that was attached to the dorsal surface of the glove. A sensor fusion algorithm computed IMU orientations based on the data from the accelerometer, gyroscope, and magnetometer. This allowed a reconstruction of the hand orientations in space and the range of the participants' wrist movements (flexion/extension, pronation/supination, ulnar/radial inclination).

EMG activity was recorded at a frequency of 1 kHz with an ANT-Neuro®Eego-sports system with shielded cables. EMG signals were recorded in a continuous way during the whole experimental session and were synchronized with the kinematic recordings thanks to a dedicated push button used at the start of each series of movement cycles. The placement of surface EMG electrodes (Ambu©BlueSensor Ag/AgCl snap bipolar electrodes, 2 cm inter-electrode distance) was individualized for each amputee based on palpation of the active muscle volumes during PHM. They were positioned on various sites of the residual limb as shown in Figure III.1. In the case of above-elbow amputees, our present analysis focused on the EMG signals recorded by electrodes placed distally to the deltoid muscles (i.e., on the sole biceps and triceps brachii muscles). As a function of the length of the residual limb, 8 to 11 pairs of electrodes were placed. For the participant with a scapulothoracic disarticulation, 12 electrode pairs were placed around the shoulder and all of them were considered. For the below-elbow amputee, 11 electrode pairs on the residual forearm were selected. Electrode positions were photographed so that they could be reproduced in the second recording session

after training.

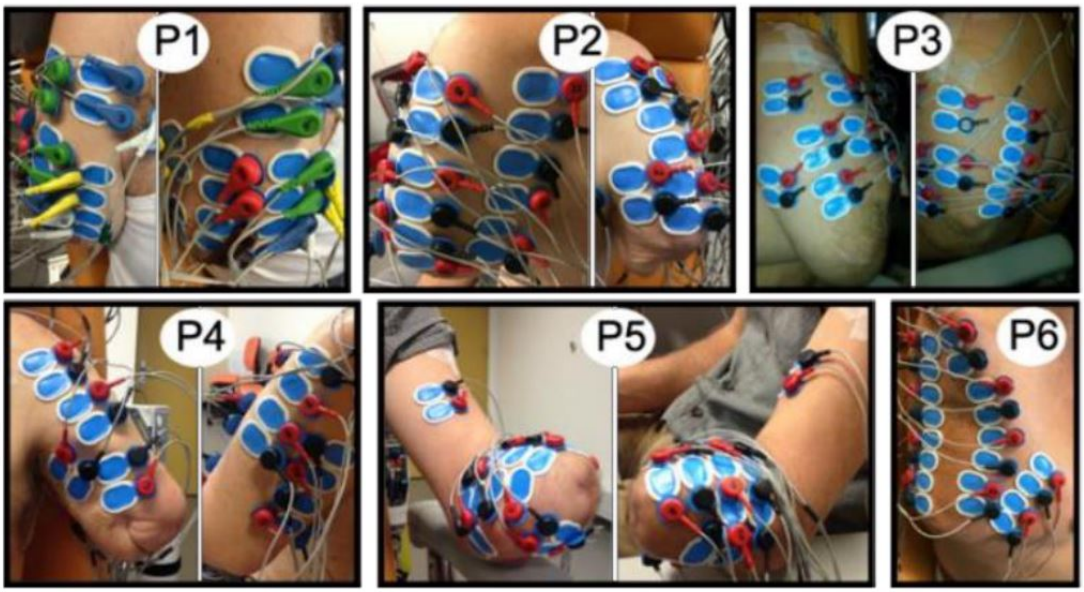

Figure III.1.: Electrode placements on the residual limb of the 6 participants. Besides for P6, two views allow visualization of almost all electrode pairs. For P1 to P4 with an above-elbow amputation, only the electrodes placed on the biceps and triceps were selected for further analyses. The ones on the deltoid, pectoralis and dorsal muscles were excluded. For P5 with a belowelbow amputation, all 11 electrodes placed on the residual forearm were selected. For P6 with a scapulothoracic amputation, all 12 electrode pairs were selected.

III.2.4. Analyses

Since flexion and extension (or opening and closing) are antagonistic movements, and thus produced by different muscle volumes, it was necessary to distinguish them in the EMG signals. Therefore, the entire kinematic and EMG analysis was based on movement half-cycles. In the following, the "number of different types of PHM" refers to all the different movements that the participant could perform, considering flexion and extension (or opening and closing) as two types of movements. Furthermore, in most analyses, the comparison of variables for initially existing movements between before (called "Pre") and after (called "Post") was made on all 10 performed cycles whether they were executed in one sequence or in different series. The new movement

types that appeared during the training period were not considered in this Pre/Post comparison since they did not undergo the exact same duration of training. However, to analyze whether these new PHM changed classification results, they were added in a separate analysis (called "PostNew") and compared to Pre and Post.

III.2.4.1. Kinematics

First, we counted the number of different types of PHM as well as the maximum number of cycles per type of PHM that each participant was able to perform without blocking. The latter measure is an indicator of susceptibility to fatigue. Then, for each participant and each type of phantom movement, we selected the specific joints involved and the kinematics was calculated by averaging the angular displacements over all the selected joints. The angular velocity was calculated as the time derivative of the recorded angles and was filtered with a third-order lowpass Butterworth filter at 2 Hz. The beginning and end of each half-cycle was identified by a change in movement direction visible in the velocity sign (see Figure III.2). For each participant, each type of phantom movement and each half-cycle, movement amplitude was computed as the difference between maximum and minimum angular displacements. Half-cycle duration and peak velocity were also extracted. To compare PHM kinematics between *Pre* and *Post*, different variables were computed and explained here-under.

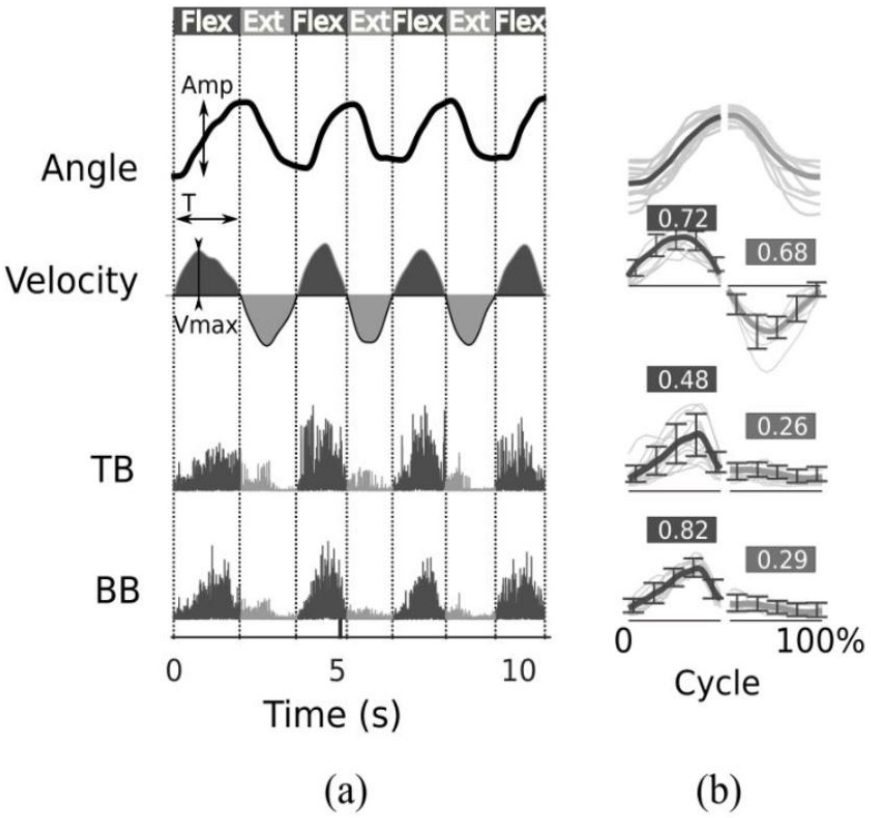

Figure III.2.: Illustration of the computation of the reproducibility indices. (a) Angle, angular velocity (upper part), EMG of the Triceps Brachial (TB) and the Biceps Brachial (BB) (lower part) for 3.5 cycles of finger flexion and extension. Separation of half-cycles was done according to the sign of the velocity signal, allowing extraction of the amplitude and peak velocity for each type of movement. (b) Temporal normalization on 100 samples per half cycle. Thin traces indicate the temporal normalized signal for all executed repetitions (i.e., mostly 10), bold traces the average over all repetitions. For the sake of clearness, standard deviations are only represented for 5 different samples. The reproducibility indices (RI-Kin and RI-EMG) calculated for this example are reported for each half-cycle above the obtained curves.

Relationship between amplitude and peak velocity For unconstrained cyclic movements, amplitude and velocity varied between cycles and between movement types, even in intact movements. Yet, what remained stable is the relationship between movement amplitude and peak velocity, the latter increasing linearly with increasing amplitude Darling et al. 1988. To investigate whether PHM training influences this

relationship, the slope β of the linear relation between peak velocity and amplitude was compared between *Pre* and *Post* for all movement types combined.

Reproducibility index (RI-Kin) As the ability to reproduce an intact limb movement is known to increase with training, the same is expected in the case of phantom movement training. Therefore, we defined a Reproducibility Index (RI) to quantify the ability to reproduce the kinematics over repetitions of a given movement. Before calculating this index, each type of movement (i.e., each half-cycle) was normalized to a time-base of 100%, containing 100 samples. This allowed us, to average the velocity signals over repetitions (bold traces in Figure III.1b). For each type m of PHM, RI^m is computed as follows:

$$RI^m = 1 - \frac{1}{100}\sum_{t=1}^{100} CoV_t^m \tag{III.1}$$

where CoV_t^m is the coefficient of variation over repetitions for velocity values at "time" t. RI^m is close to 1 if CoV_t^m averaged over "time" points is close to 0 (i.e., standard deviations are small compared to their respective mean velocity values). Some values of RI^m are reported for illustration in Figure III.1b above the velocity signal. For each participant, the global *RI-Kin* was then computed as the RI^m averaged over all movement types.

Fluidity index (FI-Kin) Before training, PHM were reported to be difficult to produce and to repeat: participants often perceived their cyclic phantom movements slowing down and sometimes eventually blocking (De Graaf et al. 2016). As with intact limb movements, the ability to produce smooth movements should increase with training, which has been suggested by some of the team's previous results Touillet et al. 2018. Smooth cyclic movements are characterized by an acceleration and deceleration phase that always precede a change in movement direction, whereas numerous accel-

eration/deceleration phases without any change of direction indicate 'non-smooth' movements. Thus, we proposed the calculation of a Fluidity Index (FI) based on the count of deceleration phases. For each movement type m, FI^m was computed as follows:

$$FI^m = 1 - \frac{1}{R}\sum_{t=1}^{R}\frac{2}{1+D_r^m} \tag{III.2}$$

Where D_r^m is the number of deceleration phases for movement type m at repetition r. R is the total number of repetitions (in general 10). If the PHM was perfectly fluid, there was only one deceleration phase per repetition: $D_r^m = 1$ so $FI^m = 1$. Figure III.3 illustrates the method of *FI* calculation performed on the velocity signal before and after training. For each participant, the global *FI-Kin* was then computed as the averaged over all movement types.

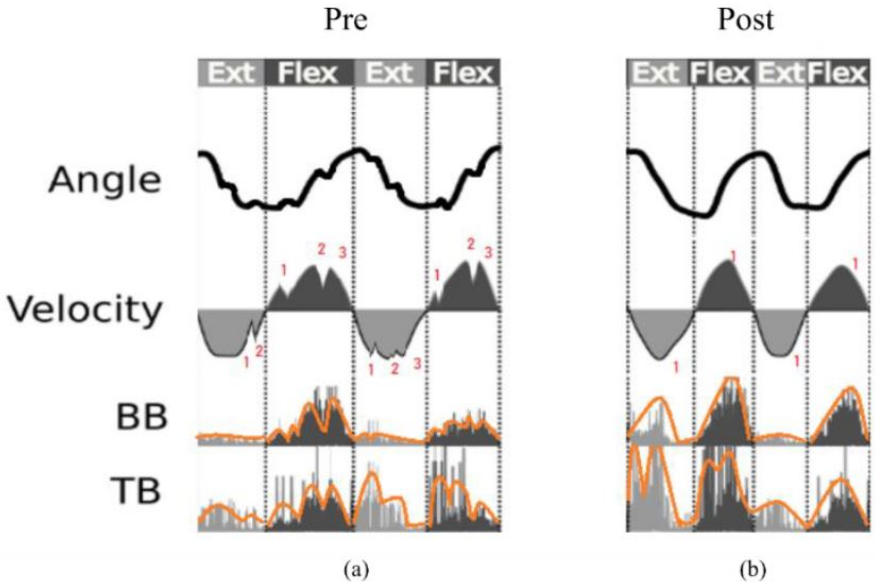

Figure III.3.: Calculation of the fluidity index, here for 2 cycles of little finger flexion and extension (a) before (Pre) and (b) after (Post) training for one participant. Upper trace: angle as a function of time. Second trace: derivative of the angle with in red, for illustration, the deceleration count. Third and fourth traces: rectified EMG signal from the BB, respectively TB, muscle, with in orange the RMS envelope.

III.2.4.2. EMG patterns

Two types of EMG signal analyses were performed. One was based on the temporal evolution of EMG amplitude and the other consisted in classifying EMG patterns (i.e., pattern recognition, PR). Both types of analyses started with filtering the recorded EMG signals with a third-order bandpass Butterworth filter between 10 Hz and 400 Hz. To distinguish EMG activity associated to PHM half-cycles, the beginning and end were identified with the help of the kinematic data (see Section IIIA Kinematics). Two variables were computed to explore the **temporal evolution** of EMG-amplitude: the EMG fluidity index (*FI-EMG*) and the EMG reproducibility index (*RI-EMG*) (see below). They were both computed before (*Pre*) and after (*Post*) training, for each type of movement. For the **classification** of EMG patterns, we used a linear discriminant analysis (LDA) classifier which is commonly used in pattern recognition algorithms (e.g., Jarrasse et al. 2018; **jarrasse_classification_2018**; Montalivet et al. 2020; Phinyomark et al. 2012). Using the above-mentioned half-cycles, each movement type was assigned to a different class. For each class, the following features were computed from the EMG: the root mean square (RMS envelope), the first 4 autoregressive coefficients, the zero crossings, the wavelength and the sample entropy (Jarrasse et al. 2018; **jarrasse_classification_2018**). Because of the extended duration of sample entropy computation, a 512-ms sliding analysis window with a 128-ms overlap between successive windows was used. To assess the possible change caused by phantom training, we used three commonly used metrics (e.g., Kristoffersen et al. 2019; Powell et al. 2014; He et al. 2015): Classification Accuracy (CA), Mean Euclidian Distances between classes (MED), and the Inter-Class Distance Nearest Neighbor (IDNN). These metrics were computed on movement types that already existed before training for both *Pre* and *Post*, as well as for all movement types including the new ones that had appeared during the training period (*PostNew*). All analyses were performed using

MATLAB software (The MathWorks, Natick, MA).

Reproducibility index (RI-EMG) The EMG reproducibility index was computed from the EMG RMS envelope of each channel in the same way as that used for kinematics (see Figure III.2). Thus, EMG signals of each type of movement (i.e., each half-cycle) and each channel was normalized to a time base of 100% such that the signals could be averaged over repetitions. RI^{mc}-EMG was defined as the reproducibility index of movement type m at EMG channel c. In Figure III.2a, the two lower traces showed EMG bursts during two cycles of finger movement measured on two distinct channel pairs on the Triceps Brachii (TB) and on the Biceps Brachii (BB). For each participant, RI^{m} represents the average of RI^{mc} over all EMG channels and the global **RI-EMG** was computed as the average of RI^{m} over all movement types.

Fluidity index (FI-EMG) While *FI-Kin* was calculated on the velocity signal, *FI-EMG* was calculated based on the RMS envelope. The number of deflections in the RMS envelope, given by the number of times the acceleration was zero, was automatically determined for each half-cycle. First, for each type m of PHM, the number of deflections for each repetition r and each EMG channel c was extracted and represented by Nd^{rcm}. FI^{mc} was defined as the fluidity index of movement type m for EMG channel c. For each participant, FI^{m} represents the average of FI^{mc} over all EMG channels and the global *FI-EMG* was computed as the average of FI^{m} over all movement types. Figure III.3 shows an example for two EMG channels.

Classification Accuracy (CA) The stability and specificity of the movement commands was assessed by the participant's ability to produce classifiable patterns. To avoid problems such as overfitting or selection bias, classification accuracy (CA) resulted from a 5-fold cross-validation (Phinyomark et al. 2012;Menon et al. 2017). Each class was divided into 5 segments of 2 full repetitions containing the same

number of classes. Four segments were used for training and the obtained decoder was applied to the remaining segment. This was done for an exhaustive number of combinations. From this, the final confusion matrix was extracted where each row represents an actual class while each column represents a predicted class. The true positive rate for the class m is CA_m, which is the diagonal of the confusion matrix. Then CA was calculated as the total true positive rate calculated over all movement types, higher CA indicating better recognition of the movement classes. The maximum score of this metric is 1.

Mean Euclidian Distance (MED) Euclidian Distance is a metric used to assess changes in the distribution of class clusters in high dimensional space. First, the Euclidian Distances between each feature centroid was computed (Powell et al. 2014; He et al. 2015). Then MED_m was defined as the Mean Euclidian inter-class Distance between centroid for the movement m and all the other classes. Finally, for each participant, the mean value was extracted to construct the *MED*.

Inter-class Distance Nearest Neighbor (IDNN) The separability of EMG patterns over different movements was quantified by the Inter-class Distance Nearest Neighbor (*IDNN*) as defined by Kristoffersen et al. 2019. It relies on the Mahalanobis distance that is currently used in pattern recognition because it measures the distance between two classes while considering the variance of each class in the space between the centroids. It therefore included the size and shape of class distributions. First, the inter-class distance between classes m_i and m_j is computed as the reduced sum of Mahalanobis distances in feature space from classes m_i and m_j. Then $IDNNm_i$ was defined as the minimum of the inter-class distances between the class m_i and all the other classes. Finally, for each participant, the *IDNN* was computed as the value of $IDNNm_i$ averaged over all types of movements.

III.2.4.3. Statistics

Statistical testing was done for each kinematic and EMG variable. The kinematic and EMG variables averaged over all movement types were not normally distributed over subjects. Thus, for group results, the median values and their corresponding 1st and 3rd quartiles were reported. The Wilcoxon paired signed-rank test was used to compare results between *Pre* and *Post*. Concerning the relationship between movement amplitude and its peak velocity, a Pearson correlation test was performed. For classification metrics, a Friedman test was performed to compare the 3 conditions *Pre*, *Post* and *PostNew*. For all tests, the significance level was set to 0.05.

III.3. Results

All 6 participants completed the training period and declared no sensation of pain in either the residual or the phantom limb during or following phantom movement executions. During our weekly phone interview, they all confirmed their daily implication in the training.

III.3.1. Kinematics

All kinematic *Pre* and *Post* data are reported in Figure 4. Overall, 5 out of the 6 participants performed more types of PHM after training than before training (group comparison $p < 0.03$, Figure III.4a; see also Table III.1). New movements had appeared 1 to 2 weeks after the beginning of training, depending on the participant. Finger movements were the ones that appeared most often. A new global hand movement around the wrist appeared in P1. For P6, movements that involved several fingers as a block before training (f2345), became individualized finger movements after training.

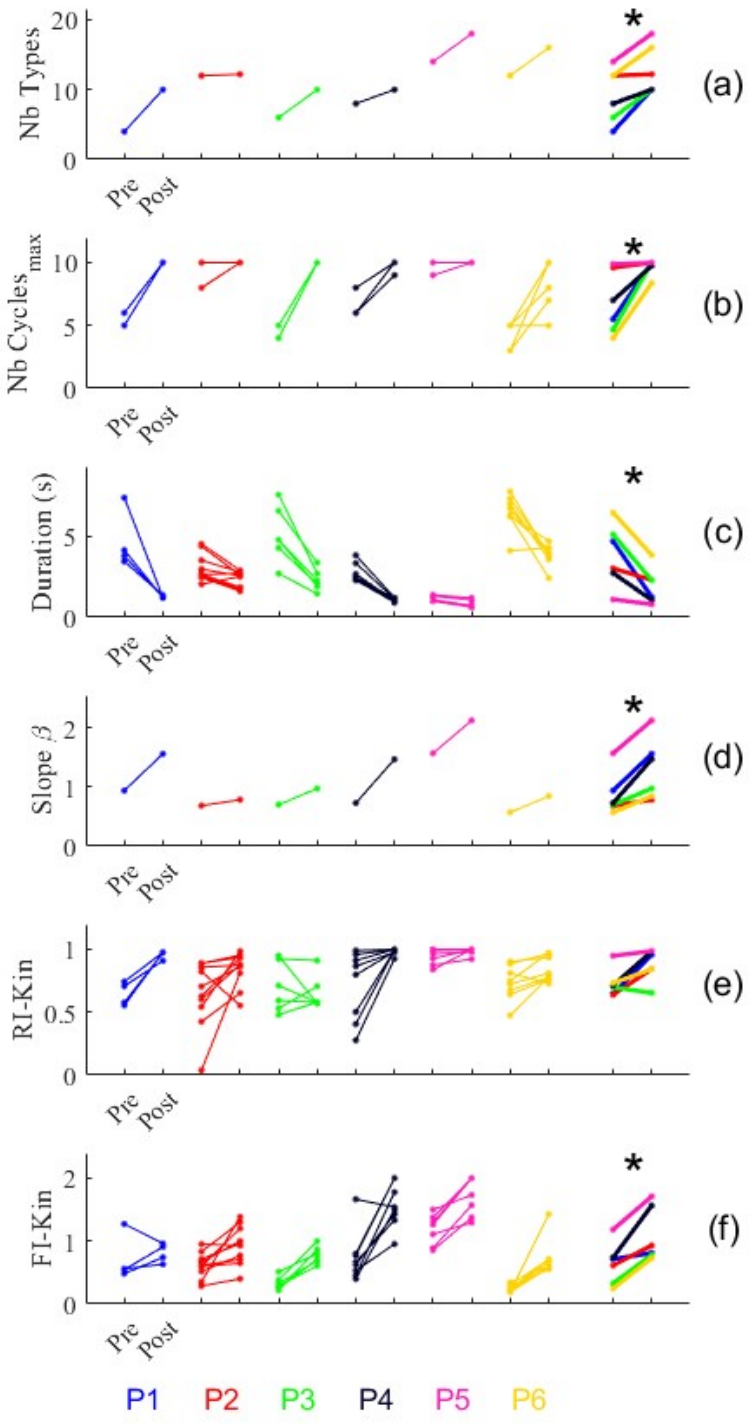

Figure III.4.: Kinematic performances for participants P1 to P6 before (*Pre*) and after a 2 month home training period (*Post*), as well as the ones averaged over all movement types for the 6 participants (right side of the figure). (a) Number of different types of PHM. (b) Number of cycles before blocking . Note that results for different movement types are sometimes superimposed. (c) Movement duratio n. (d) Slope β of amplitude/peak velocity relationship. For each participant, regressions were significant ($p < 0.001$). (e) Reproducibility index (RI-Kin). (f) Fluidity index (FI-Kin). The lines connect the results for a given PHM obtained during *Pre* and *Post* sessions. $* = p < 0.03$.

The number of cycles that could be performed in a row (i.e., without blocking) is reported in Figure III.4b. Over all participants, the median (1st-3rd quartile) number of cycles before training was 6.3 (4.9-9.7) per movement and significantly increased to 10.0 (9.4-10.0) after training ($p < 0.03$). The participants reached the number of 10 repetitions without blocking for 8 out of 10 new movements that had appeared during training.

The mean duration of movements is shown for each type of movement in the left-hand part of Figure III.4c, and as an average over all types of movement in the right-hand part of the same figure. Over all participants, the median duration dropped from 3.9 s (2.8-5.4 s) before to 1.8 s (1.0-2.7 s) after training (p<0.03). Durations for the new movements were not significantly different.

Figure III.5 shows an example of the amplitude/peak-velocity relationship for one participant: a significant positive linear relationship exists both in *Pre* and *Post* training but with a higher slope in *Post*. Thus, for a given amplitude, the peak velocity was higher after training. The group analysis confirmed these observations as it shows a significant slope increase between *Pre* and *Post* from a median value of 0.7 (0.7-0.9) to 1.2 (0.9-1.5) (p<0.03) (Figure III.4d).

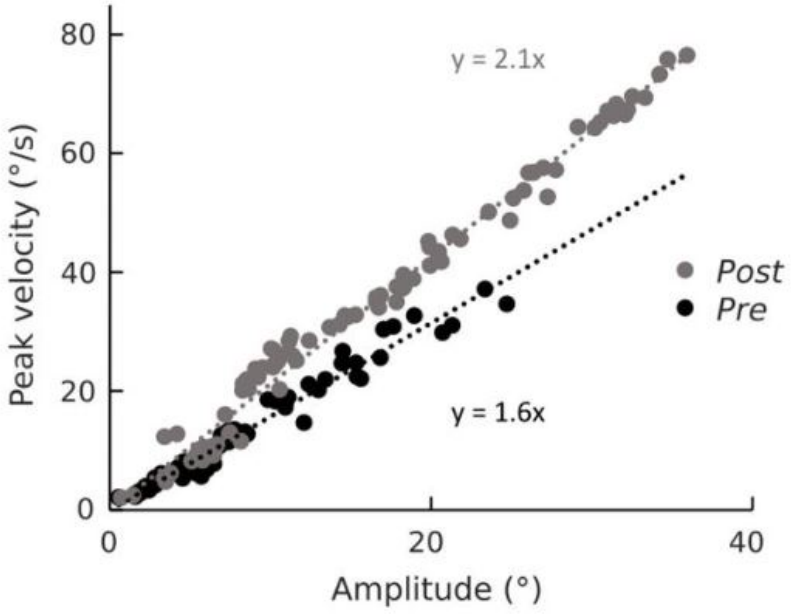

Figure III.5.: Significant amplitude/peak-velocity relationship for participant P5, *Pre* (in black) and *Post* training (in grey) ($p < 0.001$ for both regressions). Note the increase of the slope (β) after training indicating that for a given amplitude the PHM were executed at higher velocities.

Although the Reproducibility Index (*RI-Kin*) in Figure III.4e increased for many movements, globally it did not reach significance (p>0.05) mainly because of P3 whose averaged value decreased after training. The Fluidity Index (*FI-Kin*) increased from 0.7 (0.4-0.9) before training to 0.9 (0.8-1.5) after training ($p < 0.03$) (Figure III.4f). Interestingly, participant P5 - a below-elbow amputee - already had a higher number of different PHM and cycle repetitions than others before training. Yet, he still made progress in movement speed - which was shown by the decrease in cycle duration and the increase in β value - and his movements became more fluid.

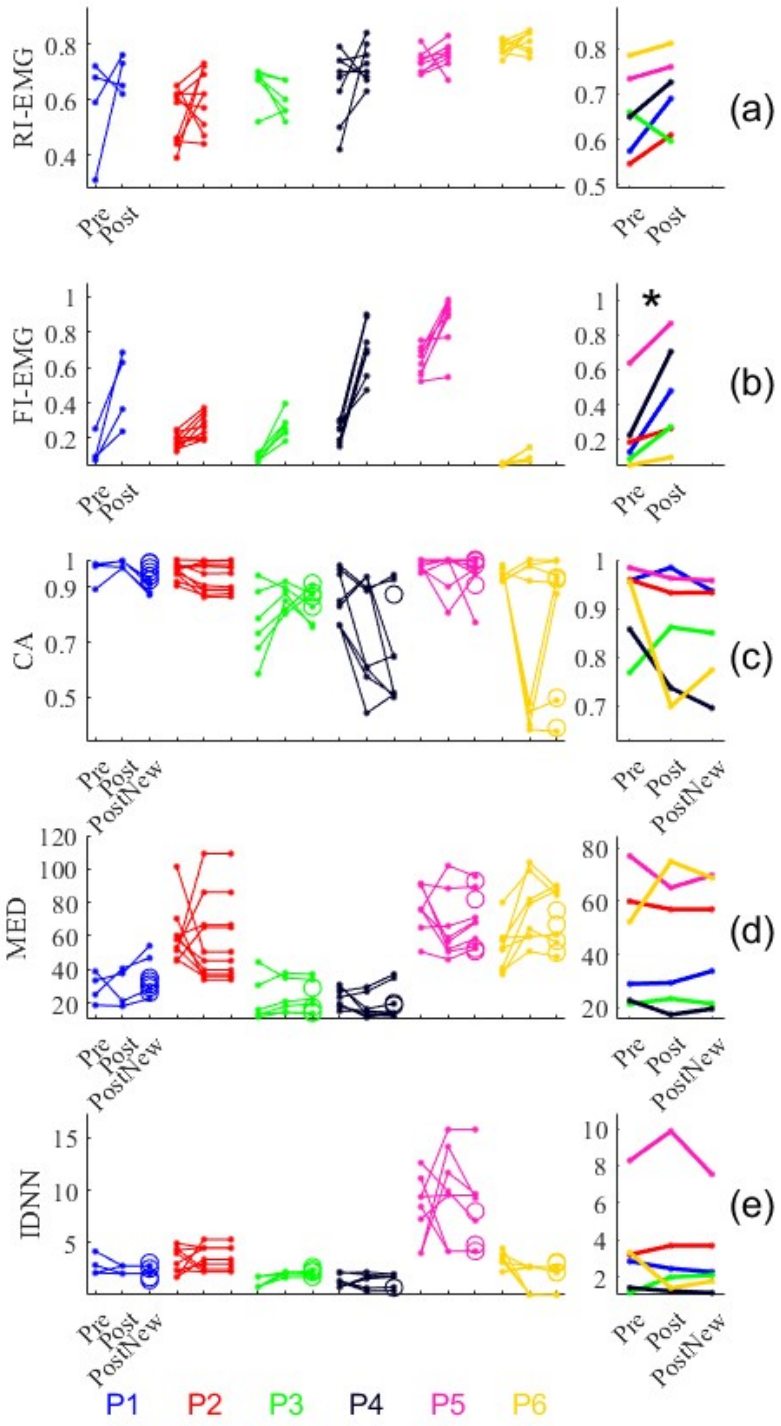

Figure III.6.: EMG feature metrics for participants P1 to P6 before (*Pre*), after a 2-month home training period (*Post*) and when integrating the new movements (*PostNew*), as well as the ones averaged over all movement types for the 6 participants (right side of the figure). Note that results for different movement types are sometimes superimposed. (a) EMG reproducibility (RI-EMG). (b) EMG fluidity (FI-EMG). (c) Classification accuracy (CA) of EMG features. (d) Mean Euclidian inter-class distances (MED). (e) Inter-class Distance Nearest Neighbor movement (IDNN). The lines connect the results for a given PHM obtained during *Pre* and *Post* sessions. The circles represent the classification metrics obtained after integration of the new movements (PostNew). $* = p < 0.05$.

III.3.2. EMG patterns

The reproducibility index (*RI-EMG*) is shown in Figure III.6a for each movement type and each participant for the *Pre* and *Post* conditions. Although all participants showed increased reproducibility after training for some movements, the group comparison showed no significant difference between the *Pre* and *Post* conditions ($p > 0.05$) because one participant (P3) had a lower average value over movements after training (Figure III.6a). On the other hand, group comparison on *FI-EMG*, represented in Figure III.6b, significantly increased after training from 0.2 (0.1-0.3) to 0.4 (0.2-0.7) ($p < 0.05$).

The results of classification analyses are shown in Figure III.6c to III.6e for all participants. Over all participants, the individual CAm values varied between 0.6 and 1.0 before training and between 0.4 and 1.0 after training. Group comparison showed no significant difference in CA, MED and IDNN values between *Pre* and *Post* sessions, even when the types of PHM that had appeared during training (*PostNew*) were included.

III.4. Discussion

The aim of this study was to examine whether daily PHM training at home for two months impacts EMG activity patterns associated with PHM in the same way as it impacts the overall phantom mobilization ability, measured from kinematic data. Participants trained all their phantom movements daily with no other feedback than somatosensory information coming from the associated contractions in residual muscles. Our results showed a significant improvement in their overall phantom mobilization ability after training. This was expressed through the increased number of types of PHM as well as the higher speed, fluidity and, for all participants but P3, reproducibility of movements. Note that the number of cycles that could be performed

in a row also increased after training, showing that susceptibility to fatigue decreased. However, although EMG bursts also became significantly smoother, none of the EMG metrics used for classification nor the reproducibility index (*RI-EMG*) improved significantly.

The team's previous results showed a decrease in cycle duration after training (Touillet et al. 2018) suggesting a faster phantom movement execution. This is confirmed and extended in the present study as the slope between amplitude and peak velocity increased with training: for a given amplitude, the peak velocity of movements became higher after training. This can be related to the fact that PHM became more fluid with training (i.e., executed in one shot without being interrupted by decelerations or stops) such that the peak velocity could reach a higher value. Interestingly, P6, who underwent a scapulothoracic disarticulation, showed kinematic characteristics close to those of above-elbow and below-elbow amputees, both before and after training. This needs yet to be confirmed through a real comparison between balanced groups of different levels of amputation. However, as far as we know, the kinematics of phantom movements had never been studied before in amputees with such high level of amputation.

Overall, our kinematic results show that phantom mobility improved with training, which should somehow correlate with modifications in EMG data. Indeed, the sensation of voluntary phantom limb movement is based on somatosensory feedback coming from movements of the residual muscles, skin, and other tissues caused by the associated muscle contractions (Reilly et al. 2006; Wu; Kaas 2000; Qi et al. 2004). Our results are consistent with this idea as, first, shorter movement durations come with shorter EMG bursts in the residual muscles after training (see time axis of Figure III.2(a) for an illustration). Second, adding the new types of PHM that the participants discovered during training as independent movements (*PostNew*) did not significantly decrease the overall classification accuracy. Adding movement classes to the classifi-

cation would have decreased its success rate if the EMG patterns associated with the new movements had resembled the ones of the already existing classes. Therefore, our results suggest that these new types of PHM are associated with EMG patterns that are distinct from the ones of already existing movements. This is consistent with the fact that the participants reported to perceive these new types of PHM as undoubtedly different from the others. Thus, improvement in the perception of phantom movement is indeed reflected in some aspects of the EMG signals.

The EMG patterns beeing classified after training on the basis of a machine learning training dataset taken before training, the absence of a significant increase of classification accuracy after training shows that EMG patterns did not fundamentally change which implies that the motor commands involved in the sensorimotor loop during PHM was not impacted by training. It confirms that PHM perception relied on the somatosensory feedback and not simply on motor intentions or memory of intact hand movements.

One might have expected the appearance of new movements to have negatively influenced CA values, which would have partly explained our results. However, we believe that this is not the case here as the new movements appeared early in the training session (after 1 to 2 weeks). In addition, we have not seen a systematic relationship between CA outcomes and the appearance of new movements. For example, P2 didn't discover new movements during training while for some movements, CA slightly decreased after training. Conversely, P3 had three new movements and its associated CA values mostly increased when comparing *Pre* and *Post* but also *Pre* and *PostNew*. Finally, if a confusion had occurred because of new movements, the overall interclass distances (*IDNN*) would have decreased for all participants but P2, which is not the case. So, overall, we consider that the new movements did not have any influence on CA.

It is important to note that before training, some CA values were already close or equal

to one. One could think of a ceiling effect that would explain why training does not allow to significantly increase CA. However, by looking more closely at the data, it can be noticed that these high values only concern some types of movements for some participants. Even for P2 and P5, who display the highest values, some are still not higher than 95% which lets some room for improvement to reach the accuracy required for everyday use. In addition, if there were a ceiling effect, the CA values would have all remained constant with training which is not the case here as some CA values in fact diminished. This decrease probably reflects the effect of confounding variables such as stress, temperature changes and general fatigue, that have long been known to influence phantom sensations in general (and thus mobility; Henderson; Smyth 1948). It is possible that their effect is strong enough to overcome the effect of our 2-month daily home training.

Additionnally, in cases where no movement was unlocked, the absence of a significant difference in classification accuracy between pre- and post-training might also be attributable to the machine learning algorithm's limitations in capturing every aspect of the signals. The algorithm was trained on a finite set of parameters, selected based on prior research in the field (Jarrasse et al. 2017a; Jarrasse et al. 2017b). As a result, it is possible that some nuances of the signals were overlooked.

The present study is conducted without a control group. However, given that without training, the kinematic aspects of phantom mobility remained stable (Touillet et al. 2018), the possible use of a control group in the present study would not have been useful. Indeed, even an increase in kinematic performance was not accompanied by an improved classification, so it seems unlikely that in a control group the classification would have evolved differently.

The type of training we chose was very different from the ones used in studies that show an increase in classification accuracy. Indeed, these studies used online visual feedback during training, that either came from an actual prosthesis (Fougner et al.

2014) or from a virtual one (Powell et al. 2014; Nakamura et al. 2017; Anderson; Bischof 2014), both inherently providing information on PR performance. If the movement of the prosthesis initiated by the decoder does not correspond to the requested movement, the user can adjust his motor command to better copy the input expected by the machine. Such movement adjustments induce modifications in the information contained in the EMG signals by changing the feature space and increasing inter-class distances. De Montalivet and colleagues (Montalivet et al. 2020) even used a pattern-similarity graphical biofeedback which gave a precise measure of the space-distance between the different EMG patterns specific to a movement type. They encouraged participants to increase this distance by finding a slightly different way of executing movements. Therefore, the most likely reason for the lack of increase in classification rate in the present study seems to be the absence of PR performance feedback during training. This hypothesis is supported by results of a study by He and colleagues (He et al. 2015) who, although focussing on static posture maintenance in mostly intact participants, did not find any improvement of classification accuracy after training without feedback on PR performance (constant "within-day error rates"). Irrespective of the exact technology or protocol used, additional feedback on PR performance seems to be necessary to increase EMG classification accuracy of phantom movements.

If so, is phantom training at home still useful to eventually increase the performance of myoelectric prostheses control? We believe it is. First, endurance of the participants is clearly enhanced by this type of training. This shows that regular use of phantom movements induces less fatigue than might have been expected from reports of amputees who had not trained their phantom movements (e.g.,Reilly et al. 2006; De Graaf et al. 2016; Kooijman et al. 2000; Raffin et al. 2016). Training allows for a high level of endurance *early* in the rehabilitation process, i.e., even before the actual use of a prosthesis. Second, the EMG bursts became more fluid and often more

reproducible. In real-life conditions, prosthesis users need the delay between their motor command and the action of the prosthesis to be as short as possible. Thus, the prosthesis must recognize a phantom movement from the start of its execution to imitate it immediately. The fact that the EMG has become more fluid and, for most of the participants, more reproducible, could prove to be an advantage when classification is performed in real time. Third, training increased the number of different types of phantom movements without penalizing classification performance. This potentially allows an increase in the number of DoF while keeping the prosthetic control intuitive. For these reasons, we encourage considering phantom mobility by training phantom movements as early as possible in the rehabilitation process.

This approach through training of PHM holds promise for mitigating residual muscle atrophy and facilitating the rapid emergence of muscle sub-volumes by stimulating potential axonal sprouting and reinnervation of residual muscle fibers by severed motoneurons. Given that peripheral neural reorganization has been found to occur during a so-called "early" period, which may persist for up to two years following complete axotomy (Delmotte et al. 2009), addressing phantom limb mobility should start promptly after amputation.

As this chapter demonstrated that improvements in phantom mobility after training are not attributed to changes in the motor commands for pre-existing movements, the following chapter explores the neural correlates of these improvements in the somatosensory feedback by investigating the representation of fingers in S1 during phantom movements.

IV. Cortical correlates of the improvement of phantom movement perception after training

IV.1. Introduction

We showed in the previous chapter that phantom movement training at home for 2 months, with no other feedback than somatosensory feedback, improved movement fluidity, reproducibility and speed. At the same time, classification accuracy was maintained while the number of movement types to be classified increased because new types of movements were released during the training process. These results tend to indicate that for the existing types of phantom movements, the motor commands have not changed and that the changes in behaviour must certainly be due to changes regarding the interpretation of the somatosensory information coming from the muscle contractions and skin movements. Movement training, whether in the form of repetitive practice, skill acquisition, or rehabilitation exercises, has been shown to induce significant changes in the brain structure and function. Due to our previous results, we decided to explore the neural correlates of the behavioural improvements

provided by our somatosensory-based home training, in the primary somatosensory cortex(S1) in particular. Understanding how movement training influences the representation of fingers in S1, through a potential reorganization, can provide insights into the plasticity of the brain. Given that training improved behavior but not the EMG patterns of preexisting phantom movements, we hypothesize that the enhancement observed in the behavioral outcomes rather comes from the phantom movements' somatosensory feedback in S1.

The cortical representation of the hand has extensively been investigated through functional magnetic resonance imaging (fMRI). fMRI detects changes in blood oxygenation levels associated with neuronal activity during a certain task, the movement of fingers in our case. When the activity of neurons increases in a particular region of the brain, the concentration of oxygenated hemoglobin increases due to bloodflow increase, leading to a detectable increase of the BOLD signal. This technique has a low temporal resolution as it only represents neural activity in an indirect manner (i.e. through bloodflow detection) but it is chosen for its high spatial resolution, serving research questions that, similarly to our case, ought to precisely localize brain activity. Thanks to this high spatial resolution, it was possible for researchers to precisely describe the representation of fingers within the hand region of S1. To detect activated patterns related to the movement of individual fingers, instead of using the "winner takes all" procedure that is starting to be called into question in its capacity to rightly depict the way body parts are represented *during movement*, we preferred to use a *dissimilarity metric* called the "Representational Similarity Analysis" (RSA). It allows researchers to compare neural activity in terms of patterns in a specific region of interest (ROI) rather than in terms of voxels and without needing to attribute each voxel to only one finger. This technique thus provides a more nuanced view than the "winner takes all" technique on how the fingers are represented in S1 during movement and how they can be altered by training.

IV.2. Methods

IV.2.1. Participants

8 participants (from 31 to 50 years old) with a traumatic unilateral amputation, either transradial or transhumeral were included in this study. To be included, they had to have phantom mobility of at least one individualized finger. Amputees who experienced phantom limb pain while performing PHM were excluded due to ethical reasons and because it limits their ability to move the phantom limb (Gagne et al. 2009). Data from 25 control participants were also used as reference on which to base the analyses.

Amputee participants were recruited at IRR (Nancy, France) and Clinique Chantecler (Marseille, France). The control participants were recruited from the research institute (MySpace Lab, Lausanne, Switzerland). The experiments were carried out in accordance with the Declaration of Helsinki of the World medical association. Written informed consent was obtained from all participants and the study received approval from a Research Ethics Committee (CPP Sud-Est I n° 22.02037.000138 (France) and CCER n° 2017-01588 (Switzerland))

IV.2.2. Protocol

The study protocol is divided into two sessions: one before the training period and the other after two months of somatosensory-based daily home training in which the participants repeated each of the phantom movements they were able to perform until blocking or until it reached 15 repetitions.

Before the first session, participants completed a structured questionnaire with the experimenter. This questionnaire was designed to assess and describe their experience of phantom limb mobility, including the frequency and vividness, but also

diverse non painful phantom sensations at rest. Both sessions followed the same fMRI experimental protocol to allow for direct comparison of neural activity before and after training. Structural images were acquired at the beginning of each session to allow for anatomical localization of the functional data. Functional imaging was then performed where participants were instructed to move or intent to move each finger of their hand individually with 6 repetitions in a row. The order of finger movements followed a specific sequence: 1-3-5-2-4, with numbers corresponding to the thumb (1) to the pinky (5). Each finger movement (or intention to move) block (12 seconds) was followed by a rest period (8 seconds). Both the phantom and intact hands were recorded one at a time. The task order was randomized across participants to prevent order effects.

IV.2.3. Data acquisition

Functional images were acquired at 7T using a T2*-weighted echo-planar imaging (EPI) sequence sensitive to blood-oxygen-level-dependent (BOLD) contrast.
Structural images were acquired using high-resolution T1-weighted 3D MP2RAGE sequences.

The velocity of movements (D1 to D5), the number of cycles that could be performed before blocking, the reported difficulty and whether the phantom movement was unlocked thanks to training was assessed. This allowed to classify, for each participants, which of the evaluated finger movements :

- remained stable after training (*stable*)
- was not unlocked with training and remained an "intention of movement" only (*intention*)
- improved with training (*improved*)

- was unlocked thanks to training (*appeared*)

IV.2.4. Analyses

The following analyses were conducted in the native space of the participants. Image preprocessing included motion correction, slice timing correction, and smoothing using a Gaussian kernel of 1mm FWHM. Spatial normalization to MNI was exclusively performed for the 25 control participants recorded only once and used as reference for the computation of the dissimilarity metric.

Data analysis was performed using a general linear model (GLM) approach to identify regions of significant activation during finger movement or movement intention. It was conducted on the smoothed images. The model (GLM1) included 5 regressors (one for each finger) convolved with the hemodynamic response, as well as the 6 rigid-body motion parameters as nuisance regressors and the framewise displacement regressor computed from these 6 rigid-body motion parameters. The F contrast extracted from this analysis and defining the functional hand area in the brain was crossed with the structure of S1 extracted from an atlas specific to each individual participant. This defined the region of interest (ROI) on which Representational Similarity Analysis (RSA) was performed. In order to perform the analysis of multivoxel activity patterns, we computed a GLM (GLM2) analysis with 30 regressors (6 repetitions x 5 fingers) and 6 rigid body motion regressors and the framewise displacement to estimate the β parameters associated with each repetition of finger movement.

Preprocessing and GLM analyses were conducted using SPM 12 software (Wellcome Department of Cognitive Neurology, London) with Matlab R2022b.

IV.2.4.1. Representational Similarity Analysis (RSA)

In order to quantify the dissimilarity between finger representation (FR) in S1 during movement, we conducted a Representationaal Similarity Analysis (RSA).
In details, RSA computes cross-validated Mahalanobis distances between activity patterns obtained from GLM2 in the Hand ROIs (for a description of GLM2, see above). For cross-validation, the 6 repetitions of the D1 to D5 movement sequence were split into even and odd repetition numbers, to form two partitions. In order to remove the effect induced by a different average activity in pre and post training, which could bias the comparison between the pattern dissimilarity of the two conditions, we removed the average activity from each condition. As the RSA was computed separately for each participant, we used bootstrapping to evaluate the variability within each participant. The RSA variable obtained, because it computes a distance, displays high values when two FR are different and low values when they are similar. More precisely, RSA quantitatively assesses the distance between the patterns of activated voxels for the 5 conditions of movements (finger D1 to D5) taken by pairs. The output is thus a 2D matrix of distances between the FR. We obtained 5x5 symmetric dissimilarity matrices for each condition pre and post training. For quantification, we summed each symmetric matrix over one dimension to obtain one RSA value per finger that measures the summed distance between each finger Dx and all the other fingers Dy. We will refer to this summed RSA as RSA_{sum} in the following. We then computed the difference $RSA_{sum}(post) - RSA_{sum}(pre)$ when appropriate.

Statistics tests were computed using RStudio running with R-4.3.2. The type of tests used are mentioned in the Results section, next to each p value.

IV.3. Results

In the control condition (i.e. movement of the intact fingers), the 2D projection of the dissimilarity matrix follows the "hand anatomy" pattern found in the litterature (Mastria et al. 2023, see Figure IV.1 for an illustration of this with P2). It thus confirms that we correctly computed the RSA metric which allows interpretation of the results regarding the phantom hand (i.e. movement of the phantom fingers). Before training, the *RSA_sum* values are significantly higher in the control condition than in the phantom condition (ANOVA shows non significative interaction between fingers and phantom/intact variable but significative principal effect of the phantom/intact variable, post hoc t test : $p = 1.4 * 10^{-9}$, see Figure IV.2). This result shows that the FR related to phantom movements' somatosensory feedback are more similar together than in the intact condition. Quite interestingly, in spite of the strong similarity between FR in the phantom condition, the 2D projection of the dissimilarity matrices follow a similar structuration as in the intact condition for most patients. When looking at the 2D projection more closely, we noted that for participants P2, P3 and P7, some FR related to phantom movements overlap before training while it is never the case of the intact condition. After training, these overlaps are reduced or disappear (see IV.1 for an illustration of this with P2). These results are not generalized to all participants tested but some improvements could also lie in a general increase of distance within patterns, without the involvement of any overlap. Thus, to quantify the improvement, we computed the difference in *RSA_sum* between post- and pre-training sessions. The results for both phantom and intact movements are compiled in Figure IV.3. Contrary to what is expected in case of improvement in movement perception, the *RSA_sum* difference between pre and post sessions are negative both for intact and phantom movements. Even through the phantom values are significantly less negative than for the intact session (ANOVA shows non singificative interaction and significative

principal effect of the phantom/intact condition, post hoc t test : $p = 1.35 * 10^{-9}$), the mean value is at best around zero. (See Figure IV.3)

In an attempt to directly link RSA results to the behavioural data, we used the categorization of finger movements and computed the median of RSA values in each category (see FigureIV.4). The movements that have appeared or improved show a higher RSA_{sum} *Pre/Post* difference than the ones that have remained stable or were just intentions of movement. Due to the limited number of points in some categories, we compiled the data into the two "positive" and "negative" behavioral groups to perform statistical testing and the results show a significative outcome (Wilcoxon Rank Summ test, $p = 0.02$)

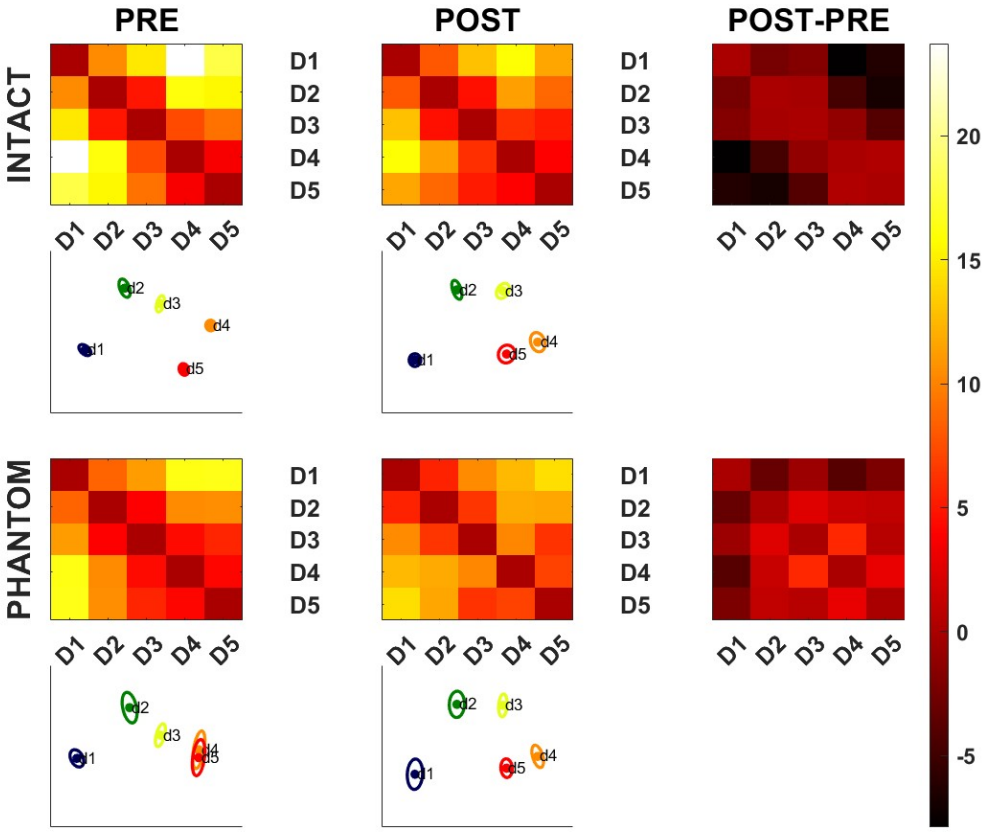

Figure IV.1.: Color matrices of RSA between fingers in pre and post for participant P2. The difference post-pre between these matrices is also displayed. The 2D representation of these matrices are displayed below each matrix with the between-trial variability of the representation of each finger (ellipses represent the standard error of the mean (SEM)). The 2D representations show a change in dissimilarity D4-D5 bettween pre and post in phantom movement, which is also seen in the post-pre matrix. : the representation of these fingers overlapped before training and are represented as distinct after training.

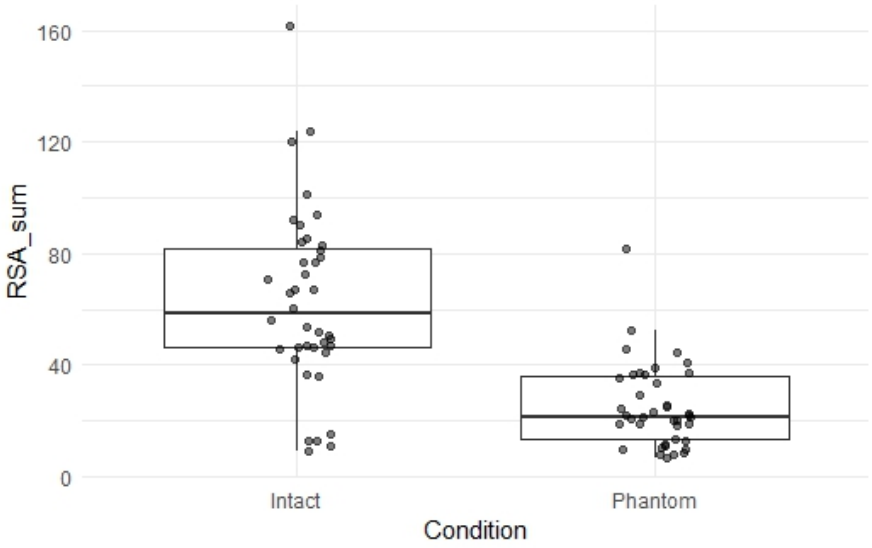

Figure IV.2.: RSA_{sum} in the phantom and intact conditions before training. In the phantom condition, they are significantly lower than in the intact condition ($p = 1.4 * 10^{-9}$). The range of values is also more extended for the intact condition.

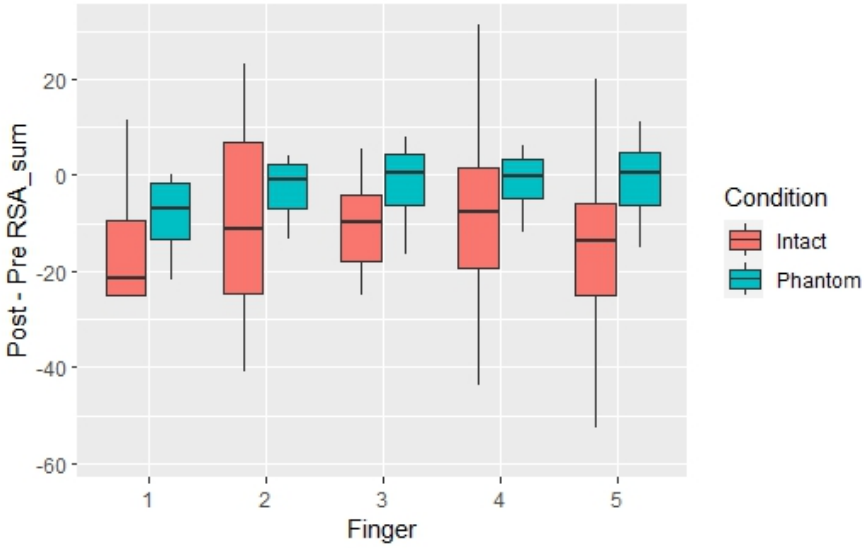

Figure IV.3.: Compilation of summed RSA values between each finger Dx after training and all the other fingers before training.

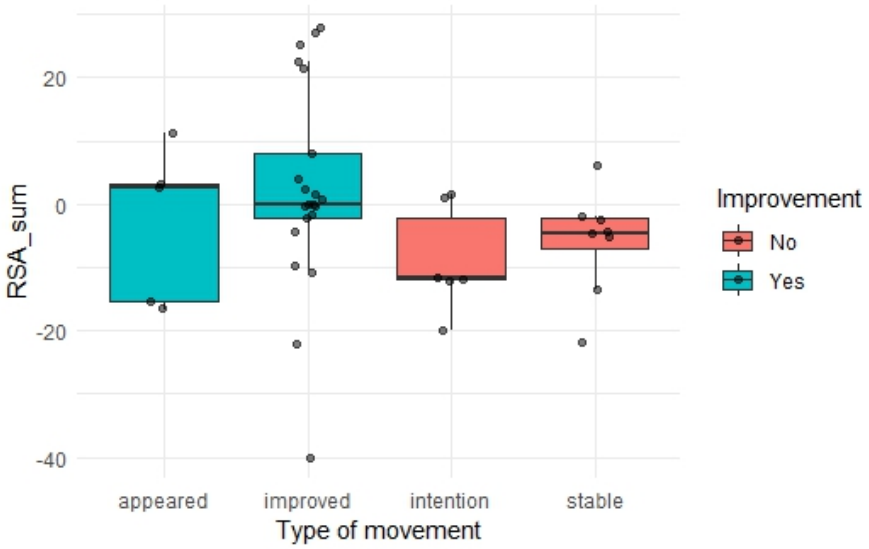

Figure IV.4.: Boxplots for classified phantom movements according to the collected behavioural results. "Intention" : movement that the participants has never been able to perform. "Appeared" : movement that has appeared with training. "Improved" : movement which perception improved with training. "Stable" : movement that has not improved with training.

IV.4. Discussion

We have shown that RSA values are significantly higher for intact movements than for phantom movements before training. This confirms that the representation of fingers in S1 are closer together after amputation, leading to a compressed representation of the five fingers within the cortical area of S1. While this miniaturization does not prevent the experience of phantom mobility, it may contribute to the slowness and difficulty often reported with these movements.

When exploring the effects of training on FR, we have seen that for the participants who displayed an overlap between some FR before training, this overlap was reduced or disappeared after training. This could indicate an effect of the training on FR associated to phantom movements which might be at the origin of the inprovements in terms of kinematics. But these results are just visualisation for a limited number

of participants. Other improvements that were not visually witnessed could be quantified. We thus computed RSA on an ROI defined on a concatenation of the pre and post session and extracted the results related to fingers in pre versus post sessions. We oberved no significative difference between intact and phantom movements in terms of pre versus post dissimilarity. The absence of improvements in the RSA values after training might be explained by the absence of improvement in terms of behaviour. Thus, we had a closer look at the behavioral data and classified the fingers into 4 categories. The "positive categories" (i.e. improved and appeared movements) displayed significantly higher values than the "negative categories".

This study suffers several limitations. First, some participants had already very good movement performance in terms of perception and kinematics before training. There might have been a ceiling effect where training could not improve the movement and thus could not lead to changes in FR. However, this ceiling effect is somewhat unlikely because we showed that the dissimilarity values between patterns are significantly lower for phantom movements than for intact movements. Furthermore, this study suffers deficiency in the monitoring of training consistency which lead some participants to train less than two month and not exactly every day. The behaviour in the fMRI machine was not monitored at all which leaves a question about the alertness of participants and the quality of their movement execution. For example, we could have used an alert button during fMRI sessions for the participant to quickly report the incorretly performed tasks and be able to retry them if necessary. Indeed, amputees are subject to fatigue and difficulties in movement execution which could significantly altered the quality of the performed movement. Finally, some participants were not able to perform some of the finger movements and might not have always performed the same motor command as an "intention of movement" which leads to problems in results interpretation as the RSA values depend on the number and thus on the nature

of the patterns taken into account in the calculation. Also, an element to take into account that cannot be worked around is the fact that when we move one finger, some motor commands are also sent to the neighbouring fingers so that they don't move along. Even though this does not provoke an actual movement in space, it involves muscle effectors and thus motor commands, seen in voxel activation and thus impacting activity patterns used by the RSA computation. Although this issue also affects the intact movement, we don't know if it affects both sides similarly and it probably affects fingers differently (it is more natural to move the thumb independently that the fourth finger). There are also some limitations related to the computation itself where the GLMs have been computed independently in pre and post session for the same participant. The calculation might have ended up in ROIs of different sizes that might have influenced the results. To solve this possible ROI problem we considered computing RSA using a GLM computed on the concatenated pre and post sessions that would have given 10x10 matrices displaying in two 5x5 pannels the distance between two FR in different sessions (pre vs post) (e.g. between D1pre and D2 post). However, this might have captured shift of patterns between pre and post that is common to all fingers, which would have had nothing to do with a change of dissimilarity between the five FR between pre and post.

Finally, the negative values on the intact side, which signify that the dissimilarity between finger representations was decreased after training, could in fact be representative of a physiological phenomenon. Some researchers have noted in studies involving intact participants that training a movement on one side only (such as the movement performed for the phantom hand in the present study) inhibitits the activity of the ipsilateral hemisphere while the contralateral hemisphere is engaged, potentially leading to persisting effects in the long term. (e.g. Tinazzi; Zanette 1998). Yet, this needs to be studied in further research.

Overall, study would need to be refined in the future to solve some of the limitations

raised above but the relationship that is shown between behavior and changes in RSA values between pre and post is an interesting lead for future research. They could open to other metrics that would better capture the observed change in dissimilarity. As the effect seems small, the study might also benefinit from a training of increased length and intensity.

General discussion

In the first chapter of this thesis, I highlighted a paradox between the existence of phantom mobility , which is known to involve the sensorimotor system, and the apparent cortical remapping that seemingly erases the representation of the amputated limb in the primary somatosensory and motor cortices (S1 and M1). To address this paradox, I decided to consider the long-neglected peripheral nervous system, dedicating two chapters to its analysis. In the first of these, I demonstrated that patterns of muscle activities on the residual limb, specifically the residual upper arm of transhumeral amputees, displayed an electrode-site specificity that could not be explained solely by cortical reorganization and could not have preexisted amputation. Instead, I proposed, based on previous results in monkeys, that neural sprouting may have occured in the residual limb after amputation, leading to the formation of muscle sub-volumes. This mechanism better explains the observed target transfer where muscles in the residual upper arm of transhumeral amputees, which were not involved in intact hand movements before amputation, become the effectors of hand motor commands in the context of phantom mobility. This aspect had never been thouroughly explored before because neglected in favor of exploration of cortical reorganization. Given that phantom mobility is often reported as difficult and slow to execute, despite the lack of physical constraints due to the absence of the limb, this approach provided an intriguing avenue for further exploration of muscle activities associated with phantom hand movements. In the subsequent chapter, given that

phantom movement training, referred to as "somatosensory training" in this thesis [1], improved several kinematic metrics and eased movement execution (see Touillet et al. 2018), I investigated whether the improvement on reported perception due to training correlated with changes in muscle activity patterns. Our hypothesis was that improvement of perception should somehow be transposed in the patterns of muscle activity as they are part of the somatosensory feedback source. I found that, even when training unlocked phantom movements that participants were previously unable to perform, the difference between the patterns of activity associated with the other movements was not altered, as indicated by the stable performance of the machine learning algorithm used to quantify alterations in the electromyographic(EMG) signals (see Chapter III). This showed that training can enlarge the "movement library" of participants but that motor commands (at the origin of the recorded muscle activity patterns) did not fundamentally change after training in spite of better fluidity, reproducibility and speed in the perception of movement. This confirms that it is not so much the motor commands and thus a putative "afference copy" directly sent to S1 that makes the perception of phantom mobility but rather the actual somatosensory feedback comming from muscle activities but also movements of the skin and other tissues. It has been previsouly shown in deafferented patients who can perform movements but do not have somatosensory feedback of these executions and thus no sensation of movement. This requires them to rely on other senses such as visual feedback (Bringoux et al. 2016). In the last chapter (chapter IV), I investigated the neural correlates of the perceived improvements in phantom mobility due to training. Given that the motor commands did change with training (see chapter IV), we investigated

[1] The most rigorous manner to train the phantom movement without somehow artificially orienting the execution of movement which might have created a mismatch between motor commands and the actual perception of movement, was to avoid using feedback on "performance" of execution and thus simply ask the participants to repeat the execution of movements by focusing on producing the perception of the specific movement at stake. In the thesis, we called this type of training "somatosensory training" in opposition to the training with performance feedback widely deployed in the context of learning how to use traditional myoelectric prostheses.

the somatosensory feedback in the primary somatosensory cortex (S1). We decided to use the movements of the 5 phantom fingers to compute a dissimilarity between their representation through their associated somatosensory feedback. In parallel, behavioural performance was monitored to be able to directly put the two sources of data (cortical and behavioural) in perspective. We found that for movements that improved or appeared after training, the pre-post difference in the distance between the representation of fingers was higher for movements with positive outcomes that those with negative outcomes.

There are numerous factors influencing the recapture of surrounding tissue by severed nerve fibers, including genetic and physiological factors. However, one factor seems particularly evident: the spatial relationship between severed nerves and the tissues of the residual limb following amputation. Currently, there is no standardized surgical procedure for limb amputations. Typically, nerves are severed by gently pulling them beyond the residual limb, allowing them to retract proximally due to their elasticity, with little attention given to their precise positioning. Yet, positioning a severed nerve on or within muscle tissue increases the likelihood of successful reinnervation (Woo et al., 2016). Moreover, in upper limb amputations, the muscles severed during the procedure are generally not reattached, either to the bone or to each other, but are left unattached before the skin closure of the residual limb. As a result, the placement of nerves relative to muscle and other surrounding tissues varies significantly between amputees. This variability may partly explain the differences observed in the onset and intensity of phantom sensations, and in particular the fact that one fourth of patients do not report any phantom mobility. If the surgical technique indeed influences nerve regeneration and tissue recapture, and these factors play a crucial role in the development of phantom sensations beneficial for prosthetic use, it could be beneficial to both standardize amputation surgery (ensuring the distal

ends of nerves are positioned to optimize reinnervation) and employ therapeutic strategies developed in recent decades to promote nerve regrowth, such as immunosuppressants, calcium channel blockers, and nerve growth factors. This still needs to be studied.

Our data collected for over 10 years suggests that phantom mobility is generally slowly developping from the day of the amputation up to two years after. This is seen through the developpement of the specificity of EMG patterns where drastic changes occur in the few months after surgery and remain stable (in spite of training as seen in Chapter III) when amputation is older than about two years. This seems to correlate with the temporal resolution of peripheral sprouting which is a slow process of trials and errors, growth and degrowth. Because of this temporal profile in the developpement phantom mobility, I believe longitudinal studies should be prioritized in the future to better capture the details of the different aspect of reorganization post amputation. This is in fact what is recommended by Makin's team which is a leading research team in the field (Schone et al. 2023). In longitudinal studies, the inhomogeneity accross patients, that cannot be overcome, can at least be controlled better because it is the same inhomogeneity at every time point for which the variables are compared. We should go further than two time points (like we did to explore the correlates of phantom mobility improvement due to training in Chapters III and IV) and the best would be to include participants even before their surgery. In France, this would imply a change of laws towards the british model where recruitment for research studies is proposed as soon as the patient enters the hospital.

Finally to go further in the precision of exploration at the periphery, I think it is crucial to explore the anatomy of residual muscles. First, it would be a way to confirm the interpretation to the present results on the existence of muscle subvolumes and it would also help to obtimize the position of EMG electrodes, both for further fundamental research and for development of prosthesis based on phantom mobility as Jarrassé

and colleagues started doing (Jarrasse et al. 2018).

In conclusion, a few remarks concerning the use of phantom limb mobility for controlling prosthetic hands are warranted. The research team has already established a proof of concept (Jarrasse et al. 2018); however, two significant challenges remain to be addressed. The first challenge pertains to the testing conditions: thus far, the prosthesis has been positioned adjacent to participants rather than being worn. Wearing the prosthesis will induce muscular activities associated with the movements of the residual limb in space during use and the resistance to the prosthesis weight. Therefore, it will be necessary to differentiate between these noisy EMG signals and the ones associated with phantom movements. This differentiation will require a robust algorithm for the detection and identification of phantom movements within the recorded noisy EMG signals. The second challenge involves understanding whether individuals with amputation will embrace this new type of prosthesis control via phantom limb mobility, and whether this phantom-based control will genuinely facilitate operation for day-to-day use.

Bibliography

ANDERSON, Fraser; BISCHOF, Walter F., 2014. Augmented reality improves myoelectric prosthesis training. *International Journal on Disability and Human Development* [online]. Vol. 13, no. 3, pp. 349–354 [visited on 2022-02-17]. ISSN 2191-0367. Available from DOI: 10.1515/ijdhd-2014-0327. Publisher: De Gruyter (cit. on pp. 70, 92).

BACHINI, Lisa; MAHÉ, Claire; TOUILLET, Amélie; LOIRET, Isabelle; HERBÉ, Pierrick; BONILLO, Isabelle; MESURE, Serge; PAYSANT, Jean; DE GRAAF, Jozina B., [n.d.]. New insights into the influence of phantom limb on gait in lower-limb amputees. *Under Review* (cit. on pp. 13, 20, 23).

BARD, Chantal; PAILLARD, Jacques; LAJOIE, Yves; FLEURY, Michelle; TEASDALE, Normand; FORGET, Robert; LAMARRE, Yves, 1992. Role of afferent information in the timing of motor commands: A comparative study with a deafferented patient. *Neuropsychologia* [online]. Vol. 30, no. 2, pp. 201–206 [visited on 2024-05-21]. ISSN 00283932. Available from DOI: 10.1016/0028-3932(92)90028-K (cit. on p. 33).

BERGMEISTER, Konstantin D.; VUJAKLIJA, Ivan; MUCELI, Silvia; STURMA, Agnes; HRUBY, Laura A.; PRAHM, Cosima; RIEDL, Otto; SALMINGER, Stefan; MANZANO-SZALAI, Krisztina; AMAN, Martin; RUSSOLD, Michael-Friedrich; HOFER, Christian; PRINCIPE, Jose; FARINA, Dario; ASZMANN, Oskar C., 2017. Broadband Prosthetic Interfaces: Combining Nerve Transfers and Implantable Multichannel EMG Technology to Decode Spinal Motor Neuron Activity. *Frontiers in Neuroscience* [online].

Vol. 11 [visited on 2022-09-26]. ISSN 1662-453X. Available from: https://www.frontiersin.org/articles/10.3389/fnins.2017.00421 (cit. on p. 61).

BRINGOUX, Lionel; SCOTTO DI CESARE, Cécile; BOREL, Liliane; MACALUSO, Thomas; SARLEGNA, Fabrice R., 2016. Do Visual and Vestibular Inputs Compensate for Somatosensory Loss in the Perception of Spatial Orientation? Insights from a Deafferented Patient. *Frontiers in Human Neuroscience* [online]. Vol. 10 [visited on 2024-10-19]. ISSN 1662-5161. Available from DOI: 10.3389/fnhum.2016.00181. Publisher: Frontiers (cit. on p. 109).

BRUGGER, Peter, 2005. From Phantom Limb to Phantom Body:Varieties of Extracorporeal Awareness. In: KNOBLICH, Gunther; THORNTON, Ian M; GROSJEAN, Marc; SHIFFRAR, Maggie (eds.). *Human Body Perception From The Inside Out* [online]. Oxford University PressNew York, NY, pp. 170–210 [visited on 2024-04-10]. ISBN 978-0-19-517837-1 978-0-19-773574-9. Available from DOI: 10.1093/oso/9780195178371.003.0009 (cit. on pp. 14, 21, 22, 29).

BUYS, E. J.; LEMON, R. N.; MANTEL, G. W.; MUIR, R. B., 1986. Selective facilitation of different hand muscles by single corticospinal neurones in the conscious monkey. *The Journal of Physiology*. Vol. 381, pp. 529–549. ISSN 0022-3751. Available from DOI: 10.1113/jphysiol.1986.sp016342 (cit. on p. 28).

CALFORD, M. B.; TWEEDALE, R., 1991. Acute changes in cutaneous receptive fields in primary somatosensory cortex after digit denervation in adult flying fox. *Journal of Neurophysiology*. Vol. 65, no. 2, pp. 178–187. ISSN 0022-3077. Available from DOI: 10.1152/jn.1991.65.2.178 (cit. on p. 35).

CATANI, Marco; DELL'ACQUA, Flavio; VERGANI, Francesco; MALIK, Farah; HODGE, Harry; ROY, Prasun; VALABREGUE, Romain; SCHOTTEN, Michel Thiebaut de, 2012. Short frontal lobe connections of the human brain. *Cortex; a Journal Devoted to the*

Study of the Nervous System and Behavior. Vol. 48, no. 2, pp. 273–291. ISSN 1973-8102. Available from DOI: 10.1016/j.cortex.2011.12.001 (cit. on p. 32).

CHEESBOROUGH, Jennifer E.; SMITH, Lauren H.; KUIKEN, Todd A.; DUMANIAN, Gregory A., 2015. Targeted Muscle Reinnervation and Advanced Prosthetic Arms. *Seminars in Plastic Surgery* [online]. Vol. 29, no. 1, pp. 62–72 [visited on 2022-02-17]. ISSN 1535-2188. Available from DOI: 10.1055/s-0035-1544166 (cit. on p. 69).

CIPRIANI, Christian; ANTFOLK, Christian; CONTROZZI, Marco; LUNDBORG, Göran; ROSEN, Birgitta; CARROZZA, Maria Chiara; SEBELIUS, Fredrik, 2011. Online myoelectric control of a dexterous hand prosthesis by transradial amputees. *IEEE transactions on neural systems and rehabilitation engineering: a publication of the IEEE Engineering in Medicine and Biology Society*. Vol. 19, no. 3, pp. 260–270. ISSN 1558-0210. Available from DOI: 10.1109/TNSRE.2011.2108667 (cit. on p. 66).

CLASSEN, Joseph; LIEPERT, Joachim; WISE, Steven P.; HALLETT, Mark; COHEN, Leonardo G., 1998. Rapid Plasticity of Human Cortical Movement Representation Induced by Practice. *Journal of Neurophysiology* [online]. Vol. 79, no. 2, pp. 1117–1123 [visited on 2024-04-11]. ISSN 0022-3077, ISSN 1522-1598. Available from DOI: 10.1152/jn.1998.79.2.1117 (cit. on p. 30).

CUNNINGHAM, David A.; MACHADO, Andre; YUE, Guang H.; CAREY, Jim R.; PLOW, Ela B., 2013. Functional somatotopy revealed across multiple cortical regions using a model of complex motor task. *Brain Research* [online]. Vol. 1531, pp. 25–36 [visited on 2024-09-13]. ISSN 0006-8993. Available from DOI: 10.1016/j.brainres.2013.07.050 (cit. on pp. 14, 28).

DARIAN-SMITH, C.; GILBERT, C. D., 1994. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature*. Vol. 368, no. 6473, pp. 737–740. ISSN 0028-0836. Available from DOI: 10.1038/368737a0 (cit. on p. 35).

DARLING, W. G.; COLE, K. J.; ABBS, J. H., 1988. Kinematic variability of grasp movements as a function of practice and movement speed. *Experimental Brain Research* [online]. Vol. 73, no. 2, pp. 225–235 [visited on 2022-02-17]. ISSN 1432-1106. Available from DOI: 10.1007/BF00248215 (cit. on p. 77).

DE GRAAF, J. B.; JARRASSE, N.; NICOL, C.; TOUILLET, A.; COYLE, T.; MAYNARD, L.; MARTINET, N.; PAYSANT, J., 2016. Phantom hand and wrist movements in upper limb amputees are slow but naturally controlled movements. *Neuroscience*. Vol. 312, pp. 48–57. ISSN 1873-7544. Available from DOI: 10.1016/j.neuroscience.2015.11.007 (cit. on pp. 23, 24, 45, 47, 48, 64, 67, 68, 73, 74, 78, 92).

DE NUNZIO, A. M.; SCHWEISFURTH, M. A.; GE, N.; FALLA, D.; HAHNE, J.; GÖDECKE, K.; PETZKE, F.; SIEBERTZ, M.; DECHENT, P.; WEISS, T.; FLOR, H.; GRAIMANN, B.; ASZMANN, O. C.; FARINA, D., 2018. Relieving phantom limb pain with multimodal sensory-motor training. *Journal of Neural Engineering*. Vol. 15, no. 6, p. 066022. ISSN 1741-2552. Available from DOI: 10.1088/1741-2552/aae271 (cit. on p. 68).

DELMOTTE, A.; RIGOARD, S.; BUFFENOIR, K.; WAGER, M.; GIOT, J. P.; ROBERT, R.; LAPIERRE, F.; RIGOARD, P., 2009. Physiologie du nerf traumatisé. *Neurochirurgie* [online]. Vol. 55, S13–S21 [visited on 2022-09-26]. ISSN 0028-3770. Available from DOI: 10.1016/j.neuchi.2008.03.010 (cit. on p. 93).

DHILLON, G. S.; KRÜGER, T. B.; SANDHU, J. S.; HORCH, K. W., 2005. Effects of Short-Term Training on Sensory and Motor Function in Severed Nerves of Long-Term Human Amputees. *Journal of Neurophysiology* [online]. Vol. 93, no. 5, pp. 2625–2633 [visited on 2024-01-18]. ISSN 0022-3077, ISSN 1522-1598. Available from DOI: 10.1152/jn.00937.2004 (cit. on pp. 37, 61).

FINGER, Stanley; HUSTWIT, Meredith P., 2003. Five Early Accounts of Phantom Limb in Context: Paré, Descartes, Lemos, Bell, and Mitchell. *Neurosurgery* [online]. Vol. 52,

no. 3, pp. 675–686 [visited on 2023-11-17]. ISSN 0148-396X. Available from DOI: 10.1227/01.NEU.0000048478.42020.97 (cit. on p. 19).

FLORENCE, S. L.; KAAS, J. H., 1995. Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*. Vol. 15, no. 12, pp. 8083–8095. ISSN 0270-6474 (cit. on pp. 15, 27, 35, 36).

FLORENCE, Sherre L.; TAUB, Hilary B.; KAAS, Jon H., 1998. Large-Scale Sprouting of Cortical Connections After Peripheral Injury in Adult Macaque Monkeys. *Science* [online]. Vol. 282, no. 5391, pp. 1117–1121 [visited on 2024-04-17]. ISSN 0036-8075, ISSN 1095-9203. Available from DOI: 10.1126/science.282.5391.1117 (cit. on p. 35).

FOUGNER, Anders L.; STAVDAHL, Øyvind; KYBERD, Peter J., 2014. System training and assessment in simultaneous proportional myoelectric prosthesis control. *Journal of NeuroEngineering and Rehabilitation* [online]. Vol. 11, no. 1, p. 75 [visited on 2022-02-17]. ISSN 1743-0003. Available from DOI: 10.1186/1743-0003-11-75 (cit. on pp. 70, 91).

GAGNE, Martin; REILLY, Karen; HETU, S; MERCIER, C, 2009. Motor control over the phantom limb in above-elbow amputees and its relationship with phantom limb pain. *Neuroscience* [online]. Vol. 162, no. 1, pp. 78–86 [visited on 2024-04-25]. ISSN 0306-4522, ISSN 1873-7544. Available from DOI: 10.1016/j.neuroscience.2009.04.061. Publisher: Elsevier (cit. on pp. 37, 42, 43, 45, 63, 68, 96).

GAGNÉ, Martin; HÉTU, Sébastien; REILLY, Karen; MERCIER, Catherine, 2011. The map is not the territory: Motor system reorganization in upper limb amputees. *Human Brain Mapping* [online]. Vol. 32, no. 4, pp. 509–519 [visited on 2022-10-12]. ISSN 10659471. Available from DOI: 10.1002/hbm.21038. Number: 4 (cit. on pp. 42, 60).

GARBARINI, Francesca; BISIO, Ambra; BIGGIO, Monica; PIA, Lorenzo; BOVE, Marco, 2018. Motor sequence learning and intermanual transfer with a phantom limb. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*. Vol. 101, pp. 181–191. ISSN 1973-8102. Available from DOI: 10.1016/j.cortex.2018.01.011 (cit. on pp. 43, 69).

GIRAUX, P.; SIRIGU, A., 2003. Illusory movements of the paralyzed limb restore motor cortex activity. *NeuroImage*. Vol. 20 Suppl 1, S107–111. ISSN 1053-8119. Available from DOI: 10.1016/j.neuroimage.2003.09.024 (cit. on pp. 20, 37).

GIRAUX, P.; SIRIGU, A.; SCHNEIDER, F.; DUBERNARD, J. M., 2001. Cortical reorganization in motor cortex after graft of both hands. *Nature Neuroscience*. Vol. 4, no. 7, pp. 691–692. ISSN 1097-6256. Available from DOI: 10.1038/89472 (cit. on p. 40).

GIUMMARRA, Melita J.; GEORGIOU-KARISTIANIS, Nellie.; NICHOLLS, Michael E. R.; GIBSON, Stephen J.; CHOU, Michael.; BRADSHAW, John L., 2010. Corporeal awareness and proprioceptive sense of the phantom. *British Journal of Psychology* [online]. Vol. 101, no. 4, pp. 791–808 [visited on 2023-11-17]. ISSN 0007-1269, ISSN 2044-8295. Available from DOI: 10.1348/000712610X492558 (cit. on pp. 21–23).

GRAAF, Jozina B. de; GALLÉA, Cécile; PAILHOUS, Jean; ANTON, Jean-Luc; ROTH, Muriel; BONNARD, Mireille, 2004. Awareness of muscular force during movement production: an fMRI study. *NeuroImage*. Vol. 21, no. 4, pp. 1357–1367. ISSN 1053-8119. Available from DOI: 10.1016/j.neuroimage.2003.11.009 (cit. on p. 67).

GUZMÁN, Rodrigo A.; SILVESTRE, Rony A.; ARRIAGADA, David A., 2011. Biceps brachii muscle innervation zone location in healthy subjects using High-Density surface electromyography. *International Journal of Morphology* [online]. Vol. 29, no. 2, pp. 347–352 [visited on 2024-04-25]. ISSN 0717-9367. Available from DOI: 10.4067/S0717-95022011000200007 (cit. on p. 61).

HE, Jiayuan; ZHANG, Dingguo; JIANG, Ning; SHENG, Xinjun; FARINA, Dario; ZHU, Xiangyang, 2015. User adaptation in long-term, open-loop myoelectric training: Implications for EMG pattern recognition in prosthesis control. *Journal of Neural Engineering* [online]. Vol. 12, no. 4 [visited on 2022-02-17]. ISSN 1741-2560. Available from DOI: 10.1088/1741-2560/12/4/046005 (cit. on pp. 80, 82, 92).

HENDERSON, W. R.; SMYTH, G. E., 1948. Phantom limbs. *Journal of Neurology, Neurosurgery, and Psychiatry*. Vol. 11, no. 2, pp. 88–112. ISSN 0022-3050. Available from DOI: 10.1136/jnnp.11.2.88 (cit. on pp. 20, 21, 37, 91).

HERMENS, H. J.; FRERIKS, B.; DISSELHORST-KLUG, C.; RAU, G., 2000. Development of recommendations for SEMG sensors and sensor placement procedures. *Journal of Electromyography and Kinesiology: Official Journal of the International Society of Electrophysiological Kinesiology*. Vol. 10, no. 5, pp. 361–374. ISSN 1050-6411. Available from DOI: 10.1016/s1050-6411(00)00027-4 (cit. on p. 47).

HOLLANDER, Myles; WOLFE, Douglas A.; CHICKEN, Eric, 2014. *Nonparametric Statistical Methods*. 3rd Edition. Hoboken, NJ: Wiley–Blackwell. ISBN 978-0-470-38737-5 (cit. on p. 53).

HUNTLEY, George W, 1997. Correlation Between Patterns of Horizontal Connectivity and the Extent of Short-term Representational Plasticity in Rat Motor Cortex (cit. on p. 35).

HUSAIN, Masud, 2022. Neural control of hand movement. *Brain* [online]. Vol. 145, no. 4, pp. 1191–1192 [visited on 2024-05-17]. ISSN 0006-8950. Available from DOI: 10.1093/brain/awac095 (cit. on p. 32).

JACOBS, Kimberle M.; DONOGHUE, John P., 1991. Reshaping the Cortical Motor Map by Unmasking Latent Intracortical Connections. *Science* [online]. Vol. 251, no. 4996, pp. 944–947 [visited on 2024-04-23]. ISSN 0036-8075, ISSN 1095-9203. Available from DOI: 10.1126/science.2000496 (cit. on p. 35).

JARRASSE, Nathanael; MONTALIVET, Etienne de; RICHER, Florian; NICOL, Caroline; TOUILLET, Amelie; MARTINET, Noel; PAYSANT, Jean; GRAAF, Jozina de, 2018. Phantom-Mobility-Based Prosthesis Control in Transhumeral Amputees Without Surgical Reinnervation: A Preliminary Study. *Frontiers in Bioengineering and Biotechnology* [online]. Vol. 6 [visited on 2022-02-17]. ISSN 2296-4185. Available from: https://www.frontiersin.org/article/10.3389/fbioe.2018.00164 (cit. on pp. 49, 62, 63, 80, 112).

JARRASSE, Nathanael; NICOL, Caroline; RICHER, Florian; TOUILLET, Amelie; MARTINET, Noel; PAYSANT, Jean; GRAAF, Jozina de, 2017a. Voluntary phantom hand and finger movements in transhumeral amputees could be used to naturally control polydigital prostheses. *arXiv:1904.11702 [physics, q-bio]* [online] [visited on 2022-02-17]. Available from: http://arxiv.org/abs/1904.11702. arXiv: 1904.11702 (cit. on pp. 15, 38, 42, 63, 65, 66, 74, 91).

JARRASSE, Nathanael; NICOL, Caroline; TOUILLET, Amelie; RICHER, Florian; MARTINET, Noel; PAYSANT, Jean; GRAAF, Jozina de, 2017b. Classification of Phantom Finger, Hand, Wrist, and Elbow Voluntary Gestures in Transhumeral Amputees With sEMG. *IEEE transactions on neural systems and rehabilitation engineering: a publication of the IEEE Engineering in Medicine and Biology Society*. Vol. 25, no. 1, pp. 68–77. ISSN 1558-0210. Available from DOI: 10.1109/TNSRE.2016.2563222 (cit. on pp. 15, 38, 42, 47, 49, 61, 65–67, 91).

JENSEN, Troels S.; KREBS, Børge; NIELSEN, Jørn; RASMUSSEN, Peter, 1983. Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation. *Pain*. Vol. 17, no. 3, pp. 243–256. ISSN 0304-3959. Available from DOI: 10.1016/0304-3959(83)90097-0 (cit. on p. 22).

JIA, Xiaofeng; KOENIG, Matthew A.; ZHANG, Xiaowen; ZHANG, Jian; CHEN, Tongyi; CHEN, Zhongwei, 2007. Residual motor signal in long-term human severed periph-

eral nerves and feasibility of neural signal-controlled artificial limb. *The Journal of Hand Surgery*. Vol. 32, no. 5, pp. 657–666. ISSN 0363-5023. Available from DOI: 10.1016/j.jhsa.2007.02.021 (cit. on p. 61).

KIKKERT, Sanne; KOLASINSKI, James; JBABDI, Saad; TRACEY, Irene; BECKMANN, Christian F.; JOHANSEN-BERG, Heidi; MAKIN, Tamar R., 2016. Revealing the neural fingerprints of a missing hand. *eLife*. Vol. 5, e15292. ISSN 2050-084X. Available from DOI: 10.7554/eLife.15292 (cit. on p. 20).

KOOIJMAN, Carolien M.; DIJKSTRA, Pieter U.; GEERTZEN, Jan H. B.; ELZINGA, Albert; SCHANS, Cees P. van der, 2000. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. *Pain*. Vol. 87, no. 1, pp. 33–41. ISSN 0304-3959. Available from DOI: 10.1016/S0304-3959(00)00264-5 (cit. on pp. 13, 20, 21, 92).

KRISTOFFERSEN, Morten B.; FRANZKE, Andreas W.; SLUIS, Corry K. van der; MURGIA, Alessio; BONGERS, Raoul M., 2019. The Effect of Feedback During Training Sessions on Learning Pattern-Recognition-Based Prosthesis Control. *IEEE transactions on neural systems and rehabilitation engineering: a publication of the IEEE Engineering in Medicine and Biology Society*. Vol. 27, no. 10, pp. 2087–2096. ISSN 1558-0210. Available from DOI: 10.1109/TNSRE.2019.2929917 (cit. on pp. 80, 82).

LAPASH DANIELS, Christine M.; AYERS, Kathryn L.; FINLEY, Amanda M.; CULVER, Joseph P.; GOLDBERG, Mark P., 2009. Axon sprouting in adult mouse spinal cord after motor cortex stroke. *Neuroscience Letters*. Vol. 450, no. 2, pp. 191–195. ISSN 0304-3940. Available from DOI: 10.1016/j.neulet.2008.11.017 (cit. on p. 31).

LEMON, R. N.; MANTEL, G. W.; MUIR, R. B., 1986. Corticospinal facilitation of hand muscles during voluntary movement in the conscious monkey. *The Journal of Physiology*. Vol. 381, pp. 497–527. ISSN 0022-3751. Available from DOI: 10.1113/jphysiol.1986.sp016341 (cit. on p. 28).

LEYTON, A. S. F.; SHERRINGTON, C. S., 1917. Observations on the Excitable Cortex of the Chimpanzee, Orang-Utan, and Gorilla. *Quarterly Journal of Experimental Physiology* [online]. Vol. 11, no. 2, pp. 135–222 [visited on 2024-09-16]. ISSN 1469-445X. Available from DOI: 10.1113/expphysiol.1917.sp000240. _eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1113/expphysiol.1917.sp000240 (cit. on pp. 14, 29).

LIEPERT, J.; TERBORG, C.; WEILLER, C., 1999. Motor plasticity induced by synchronized thumb and foot movements. *Experimental Brain Research* [online]. Vol. 125, no. 4, pp. 435–439 [visited on 2024-04-11]. ISSN 0014-4819, ISSN 1432-1106. Available from DOI: 10.1007/s002210050700 (cit. on pp. 14, 30).

LOTZE, M.; FLOR, H.; GRODD, W.; LARBIG, W.; BIRBAUMER, N., 2001. Phantom movements and pain. An fMRI study in upper limb amputees. *Brain: A Journal of Neurology*. Vol. 124, no. Pt 11, pp. 2268–2277. ISSN 0006-8950. Available from DOI: 10.1093/brain/124.11.2268 (cit. on p. 60).

MACIVER, K.; LLOYD, D. M.; KELLY, S.; ROBERTS, N.; NURMIKKO, T., 2008. Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. *Brain* [online]. Vol. 131, no. 8, pp. 2181–2191 [visited on 2024-04-30]. ISSN 0006-8950. Available from DOI: 10.1093/brain/awn124 (cit. on p. 37).

MAKIN, Tamar R.; CRAMER, Alona O.; SCHOLZ, Jan; HAHAMY, Avital; HENDERSON SLATER, David; TRACEY, Irene; JOHANSEN-BERG, Heidi, 2013. Deprivation-related and use-dependent plasticity go hand in hand. *eLife*. Vol. 2, e01273. ISSN 2050-084X. Available from DOI: 10.7554/eLife.01273 (cit. on p. 43).

MAKIN, Tamar R; KRAKAUER, John W, 2024. Against cortical reorganisation. *eLife* [online]. Vol. 12, e84716 [visited on 2024-05-02]. ISSN 2050-084X. Available from DOI: 10.7554/eLife.84716 (cit. on p. 36).

MAKIN, Tamar R.; SCHOLZ, Jan; HENDERSON SLATER, David; JOHANSEN-BERG, Heidi; TRACEY, Irene, 2015. Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation. *Brain: A Journal of Neurology*. Vol. 138, no. Pt 8, pp. 2140–2146. ISSN 1460-2156. Available from DOI: 10.1093/brain/awv161 (cit. on p. 20).

MANGER, P. R.; WOODS, T. M.; JONES, E. G., 1996. Plasticity of the somatosensory cortical map in macaque monkeys after chronic partial amputation of a digit. *Proceedings. Biological Sciences*. Vol. 263, no. 1372, pp. 933–939. ISSN 0962-8452. Available from DOI: 10.1098/rspb.1996.0138 (cit. on p. 36).

MARCONI, Barbara; PECCHIOLI, Cristiano; KOCH, Giacomo; CALTAGIRONE, Carlo, 2007. Functional overlap between hand and forearm motor cortical representations during motor cognitive tasks. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*. Vol. 118, no. 8, pp. 1767–1775. ISSN 1388-2457. Available from DOI: 10.1016/j.clinph.2007.04.028 (cit. on pp. 14, 28).

MASSÉ-ALARIE, Hugo; BERGIN, Michael J.G.; SCHNEIDER, Cyril; SCHABRUN, Siobhan; HODGES, Paul W., 2017. "Discrete peaks" of excitability and map overlap reveal task-specific organization of primary motor cortex for control of human forearm muscles. *Human Brain Mapping* [online]. Vol. 38, no. 12, pp. 6118–6132 [visited on 2024-04-15]. ISSN 1065-9471, ISSN 1097-0193. Available from DOI: 10.1002/hbm.23816 (cit. on p. 28).

MASTRIA, Giulio; SCALITI, Eugenio; MEHRING, Carsten; BURDET, Etienne; BECCHIO, Cristina; SERINO, Andrea; AKSELROD, Michel, 2023. Morphology, Connectivity, and Encoding Features of Tactile and Motor Representations of the Fingers in the Human Precentral and Postcentral Gyrus. *Journal of Neuroscience* [online]. Vol. 43, no. 9, pp. 1572–1589 [visited on 2024-10-20]. ISSN 0270-6474, ISSN 1529-2401. Available

from DOI: 10.1523/JNEUROSCI.1976-21.2022. Publisher: Society for Neuroscience Section: Research Articles (cit. on p. 100).

MCKIERNAN, B. J.; MARCARIO, J. K.; KARRER, J. H.; CHENEY, P. D., 1998. Corticomotoneuronal postspike effects in shoulder, elbow, wrist, digit, and intrinsic hand muscles during a reach and prehension task. *Journal of Neurophysiology*. Vol. 80, no. 4, pp. 1961–1980. ISSN 0022-3077. Available from DOI: 10.1152/jn.1998.80.4.1961 (cit. on pp. 28, 42).

MELZACK, Ronald, 1992. Phantom limbs. *SCIENTIFIC AMERICAN* (cit. on pp. 15, 39).

MENON, Radhika; DI CATERINA, Gaetano; LAKANY, Heba; PETROPOULAKIS, Lykourgos; CONWAY, Bernard A.; SORAGHAN, John J., 2017. Study on Interaction Between Temporal and Spatial Information in Classification of EMG Signals for Myoelectric Prostheses. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*. Vol. 25, no. 10, pp. 1832–1842. ISSN 1558-0210. Available from DOI: 10.1109/TNSRE.2017.2687761. Conference Name: IEEE Transactions on Neural Systems and Rehabilitation Engineering (cit. on p. 81).

MERCIER, Catherine; REILLY, Karen; VARGAS, Claudia D.; ABALLEA, Antoine; SIRIGU, Angela, 2006. Mapping phantom movement representations in the motor cortex of amputees. *Brain: A Journal of Neurology*. Vol. 129, no. Pt 8, pp. 2202–2210. ISSN 1460-2156. Available from DOI: 10.1093/brain/awl180 (cit. on p. 60).

MERZENICH, Michael M.; NELSON, Randall J.; STRYKER, Michael P.; CYNADER, Max S.; SCHOPPMANN, Axel; ZOOK, John M., 1984. Somatosensory cortical map changes following digit amputation in adult monkeys. *Journal of Comparative Neurology* [online]. Vol. 224, no. 4, pp. 591–605 [visited on 2024-04-23]. ISSN 0021-9967, ISSN 1096-9861. Available from DOI: 10.1002/cne.902240408 (cit. on p. 35).

MERZENICH, M.M.; KAAS, J.H.; WALL, J.T.; SUR, M.; NELSON, R.J.; FELLEMAN, D.J., 1983. Progression of change following median nerve section in the cortical represen-

tation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. *Neuroscience* [online]. Vol. 10, no. 3, pp. 639–665 [visited on 2024-04-16]. ISSN 03064522. Available from DOI: 10.1016/0306-4522(83)90208-7 (cit. on p. 34).

MITCHELL, Silas Weir, 1866. The Case of George Dedlow. *The Atlantic Monthly* (cit. on p. 19).

MITCHELL, Silas Weir, 1872. Neural maladies of stumps, in Injuries of Nerves and their Consequences. *Philadelphia : J.B. Lippincott & Co.* (Cit. on p. 19).

MONTALIVET, Etienne de; BAILLY, Kevin; TOUILLET, Amelie; MARTINET, Noel; PAYSANT, Jean; JARRASSE, Nathanael, 2020. Guiding the Training of Users With a Pattern Similarity Biofeedback to Improve the Performance of Myoelectric Pattern Recognition. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*. Vol. 28, no. 8, pp. 1731–1741. ISSN 1558-0210. Available from DOI: 10.1109/TNSRE.2020.3003077. Conference Name: IEEE Transactions on Neural Systems and Rehabilitation Engineering (cit. on pp. 70, 80, 92).

NAKAMURA, Go; SHIBANOKI, Taro; KURITA, Yuichi; HONDA, Yuichiro; MASUDA, Akito; MIZOBE, Futoshi; CHIN, Takaaki; TSUJI, Toshio, 2017. A virtual myoelectric prosthesis training system capable of providing instructions on hand operations: *International Journal of Advanced Robotic Systems* [online] [visited on 2022-02-17]. Available from DOI: 10.1177/1729881417728452. Publisher: SAGE Publications Sage UK: London, England (cit. on pp. 70, 92).

NAMBU, Atsushi, 2011. Somatotopic organization of the primate Basal Ganglia. *Frontiers in Neuroanatomy*. Vol. 5, p. 26. ISSN 1662-5129. Available from DOI: 10.3389/fnana.2011.00026 (cit. on pp. 14, 30).

NAVARRO, X.; VIVÓ, Meritxell; VALERO-CABRÉ, Antoni, 2007. Neural plasticity after peripheral nerve injury and regeneration. *Progress in Neurobiology*. Vol. 82, no. 4,

pp. 163–201. ISSN 0301-0082. Available from DOI: 10.1016/j.pneurobio.2007.06.005 (cit. on p. 60).

NOWAK, D. A., 2004. How predictive is grip force control in the complete absence of somatosensory feedback? *Brain* [online]. Vol. 127, no. 1, pp. 182–192 [visited on 2024-05-21]. ISSN 1460-2156. Available from DOI: 10.1093/brain/awh016 (cit. on p. 33).

OJEMANN, J. G.; SILBERGELD, D. L., 1995. Cortical stimulation mapping of phantom limb rolandic cortex. Case report. *Journal of Neurosurgery*. Vol. 82, no. 4, pp. 641–644. ISSN 0022-3085. Available from DOI: 10.3171/jns.1995.82.4.0641 (cit. on p. 60).

OLINSKI, Michał; LEWANDOWSKI, Bogusz; GRONOWICZ, Antoni, 2015. Type synthesis and preliminary design of devices supporting lower limb's rehabilitation. *Acta of Bioengineering and Biomechanics*. Vol. 17, no. 1, pp. 117–127. ISSN 1509-409X (cit. on p. 32).

ORTIZ-CATALAN, Max; GUÐMUNDSDÓTTIR, Rannveig A.; KRISTOFFERSEN, Morten B.; ZEPEDA-ECHAVARRIA, Alejandra; CAINE-WINTERBERGER, Kerstin; KULBACKA-ORTIZ, Katarzyna; WIDEHAMMAR, Cathrine; ERIKSSON, Karin; STOCKSELIUS, Anita; RAGNÖ, Christina; PIHLAR, Zdenka; BURGER, Helena; HERMANSSON, Liselotte, 2016. Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: a single group, clinical trial in patients with chronic intractable phantom limb pain. *Lancet (London, England)*. Vol. 388, no. 10062, pp. 2885–2894. ISSN 1474-547X. Available from DOI: 10.1016/S0140-6736(16)31598-7 (cit. on p. 68).

PARÉ, Ambroise, 1575. Les oeuvres de M. Ambroise Paré. In: *Les Œuvres de M. Ambroise Paré*. Paris Buon (cit. on p. 19).

PATINO, Luis; CHAKAROV, Vihren; SCHULTE-MÖNTING, Jürgen; HEPP-REYMOND, Marie-Claude; KRISTEVA, Rumyana, 2006. Oscillatory cortical activity during a

motor task in a deafferented patient. *Neuroscience Letters* [online]. Vol. 401, no. 3, pp. 214–218 [visited on 2024-05-21]. ISSN 03043940. Available from DOI: 10.1016/j.neulet.2006.03.027 (cit. on p. 33).

PENFIELD, Wilder; BOLDREY, Edwin, 1937. SOMATIC MOTOR AND SENSORY REPRESENTATION IN THE CEREBRAL CORTEX OF MAN AS STUDIED BY ELECTRICAL STIMULATION. *Brain* [online]. Vol. 60, no. 4, pp. 389–443 [visited on 2024-03-04]. ISSN 0006-8950, ISSN 1460-2156. Available from DOI: 10.1093/brain/60.4.389 (cit. on pp. 14, 26).

PENFIELD, Wilder; JASPER, Herbert, 1954. *Epilepsy and the functional anatomy of the human brain*. Oxford, England: Little, Brown & Co. Epilepsy and the functional anatomy of the human brain. Pages: xv, 896 (cit. on pp. 14, 27, 30).

PENFIELD, Wilder; RASMUSSEN, Theodore, 1950. *The cerebral cortex of man; a clinical study of localization of function*. Oxford, England: Macmillan. The cerebral cortex of man; a clinical study of localization of function. Pages: xv, 248 (cit. on pp. 14, 27).

PHINYOMARK, Angkoon; PHUKPATTARANONT, Pornchai; LIMSAKUL, Chusak, 2012. Feature reduction and selection for EMG signal classification. *Expert Systems with Applications* [online]. Vol. 39, no. 8, pp. 7420–7431 [visited on 2022-02-17]. ISSN 0957-4174. Available from DOI: 10.1016/j.eswa.2012.01.102 (cit. on pp. 80, 81).

PIASECKI, Mathew; IRELAND, Alex; JONES, David A.; MCPHEE, Jamie S., 2016. Age-dependent motor unit remodelling in human limb muscles. *Biogerontology* [online]. Vol. 17, no. 3, pp. 485–496 [visited on 2024-04-25]. ISSN 1573-6768. Available from DOI: 10.1007/s10522-015-9627-3 (cit. on p. 64).

PLOW, Ela B.; ARORA, Pooja; PLINE, Megan A.; BINENSTOCK, Meagan T.; CAREY, James R., 2010. Within-limb somatotopy in primary motor cortex – revealed using fMRI. *Cortex* [online]. Vol. 46, no. 3, pp. 310–321 [visited on 2024-09-13]. ISSN 00109452. Available from DOI: 10.1016/j.cortex.2009.02.024 (cit. on p. 28).

PONS, Tim P.; GARRAGHTY, Preston E.; OMMAYA, Alexander K.; KAAS, Jon H.; TAUB, Edward; MISHKIN, Mortimer, 1991. Massive Cortical Reorganization After Sensory Deafferentation in Adult Macaques. *Science* [online]. Vol. 252, no. 5014, pp. 1857–1860 [visited on 2024-04-16]. ISSN 0036-8075, ISSN 1095-9203. Available from DOI: 10.1126/science.1843843 (cit. on pp. 15, 34, 35).

POWELL, Michael A.; KALIKI, Rahul R.; THAKOR, Nitish V., 2014. User training for pattern recognition-based myoelectric prostheses: Improving phantom limb movement consistency and distinguishability. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* [online]. Vol. 22, no. 3, pp. 522–532 [visited on 2022-02-17]. ISSN 1534-4320. Available from DOI: 10.1109/TNSRE.2013.2279737. Publisher: Institute of Electrical and Electronics Engineers Inc. (cit. on pp. 70, 80, 82, 92).

QI, Hui-Xin; STEWART PHILLIPS, W.; KAAS, Jon H., 2004. Connections of neurons in the lumbar ventral horn of spinal cord are altered after long-standing limb loss in a macaque monkey. *Somatosensory & Motor Research*. Vol. 21, no. 3-4, pp. 229–239. ISSN 0899-0220. Available from DOI: 10.1080/08990220400012588 (cit. on pp. 61, 89).

RAFFIN, Estelle; GIRAUX, Pascal; REILLY, Karen, 2012a. The moving phantom: Motor execution or motor imagery? *Cortex* [online]. Vol. 48, no. 6, pp. 746–757 [visited on 2023-11-17]. ISSN 00109452. Available from DOI: 10.1016/j.cortex.2011.02.003 (cit. on p. 37).

RAFFIN, Estelle; MATTOUT, Jérémie; REILLY, Karen; GIRAUX, Pascal, 2012b. Disentangling motor execution from motor imagery with the phantom limb. *Brain: A Journal of Neurology*. Vol. 135, no. Pt 2, pp. 582–595. ISSN 1460-2156. Available from DOI: 10.1093/brain/awr337 (cit. on pp. 15, 38, 41).

RAFFIN, Estelle; RICHARD, Nathalie; GIRAUX, Pascal; REILLY, Karen, 2016. Primary motor cortex changes after amputation correlate with phantom limb pain and the

ability to move the phantom limb. *NeuroImage* [online]. Vol. 130, pp. 134–144 [visited on 2024-01-18]. ISSN 10538119. Available from DOI: 10.1016/j.neuroimage.2016.01.063 (cit. on p. 92).

RAMACHANDRAN, V S; HIRSTEIN, W, 1998. The perception of phantom limbs. The D. O. Hebb lecture. *Brain* [online]. Vol. 121, no. 9, pp. 1603–1630 [visited on 2023-11-17]. ISSN 0006-8950. Available from DOI: 10.1093/brain/121.9.1603 (cit. on pp. 21, 22).

RASMUSSON, Douglas D., 1982. Reorganization of raccoon somatosensory cortex following removal of the fifth digit. *Journal of Comparative Neurology* [online]. Vol. 205, no. 4, pp. 313–326 [visited on 2024-09-17]. ISSN 1096-9861. Available from DOI: 10.1002/cne.902050402. _eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1002/cne.902050402 (cit. on p. 35).

REILLY, Karen; MERCIER, Catherine; SCHIEBER, Marc; SIRIGU, Angela, 2006. Persistent hand motor commands in the amputees' brain. *Brain: A Journal of Neurology*. Vol. 129, no. Pt 8, pp. 2211–2223. ISSN 1460-2156. Available from DOI: 10.1093/brain/awl154 (cit. on pp. 14, 37, 38, 41, 42, 45, 63, 89, 92).

REILLY, Karen; SIRIGU, Angela, 2008. The Motor Cortex and Its Role in Phantom Limb Phenomena. *The Neuroscientist* [online]. Vol. 14, no. 2, pp. 195–202 [visited on 2023-11-17]. ISSN 1073-8584. Available from DOI: 10.1177/1073858407309466. Publisher: SAGE Publications Inc STM (cit. on pp. 15, 39).

RIDDOCH, George, 1941. PHANTOM LIMBS AND BODY SHAPE [1]. *Brain* [online]. Vol. 64, no. 4, pp. 197–222 [visited on 2024-04-04]. ISSN 0006-8950, ISSN 1460-2156. Available from DOI: 10.1093/brain/64.4.197 (cit. on pp. 20, 22, 23).

ROSÉN, G.; HUGDAHL, K.; ERSLAND, L.; LUNDERVOLD, A.; SMIEVOLL, A. I.; BARNDON, R.; SUNDBERG, H.; THOMSEN, T.; ROSCHER, B. E.; TJØLSEN, A.; ENGELSEN, B., 2001. Different brain areas activated during imagery of painful and non-painful

'finger movements' in a subject with an amputated arm. *Neurocase*. Vol. 7, no. 3, pp. 255–260. ISSN 1355-4794. Available from DOI: 10.1093/neucas/7.3.255 (cit. on p. 37).

ROUX, Franck-Emmanuel; DJIDJELI, Imène; DURAND, Jean-Baptiste, 2018. Functional architecture of the somatosensory homunculus detected by electrostimulation. *The Journal of Physiology* [online]. Vol. 596, no. 5, pp. 941–956 [visited on 2024-04-10]. ISSN 0022-3751, ISSN 1469-7793. Available from DOI: 10.1113/JP275243 (cit. on pp. 14, 27).

SALA, Francesco, 2018. Penfield's stimulation for direct cortical motor mapping: An outdated technique? *Clinical Neurophysiology* [online]. Vol. 129, no. 12, pp. 2635–2637 [visited on 2024-03-21]. ISSN 13882457. Available from DOI: 10.1016/j.clinph.2018.09.021 (cit. on p. 27).

SANES, Jerome N.; DONOGHUE, John P., 2000. Plasticity and Primary Motor Cortex. *Annual Review of Neuroscience* [online]. Vol. 23, no. 1, pp. 393–415 [visited on 2024-03-25]. ISSN 0147-006X, ISSN 1545-4126. Available from DOI: 10.1146/annurev.neuro.23.1.393 (cit. on pp. 14, 28).

SARLEGNA, Fabrice R.; GAUTHIER, Gabriel M.; BOURDIN, Christophe; VERCHER, Jean-Louis; BLOUIN, Jean, 2006. Internally driven control of reaching movements: A study on a proprioceptively deafferented subject. *Brain Research Bulletin* [online]. Vol. 69, no. 4, pp. 404–415 [visited on 2024-05-21]. ISSN 03619230. Available from DOI: 10.1016/j.brainresbull.2006.02.005 (cit. on p. 33).

SCALITI, Eugenio; GRUPPIONI, Emanuele; BECCHIO, Cristina, 2020. And Yet It Moves: What We Currently Know about Phantom Arm Movements. *The Neuroscientist* [online]. Vol. 26, no. 4, pp. 328–342 [visited on 2023-11-17]. ISSN 1073-8584, ISSN 1089-4098. Available from DOI: 10.1177/1073858420904326 (cit. on p. 37).

SCHIEBER, Marc H., 2001. Constraints on Somatotopic Organization in the Primary Motor Cortex. *Journal of Neurophysiology* [online]. Vol. 86, no. 5, pp. 2125–2143 [visited on 2024-03-25]. ISSN 0022-3077, ISSN 1522-1598. Available from DOI: 10.1152/jn.2001.86.5.2125 (cit. on pp. 14, 28).

SCHONE, Hunter R.; MAIMON MOR, Roni O.; KOLLAMKULAM, Mathew; GERRAND, Craig; WOOLLARD, Alexander; KANG, Norbert V.; BAKER, Chris I.; MAKIN, Tamar R., 2023. Stable Cortical Body Maps Before and After Arm Amputation. *bioRxiv* [online], p. 2023.12.13.571314 [visited on 2024-05-02]. Available from DOI: 10.1101/2023.12.13.571314 (cit. on pp. 36, 111).

SCHWARTZ, Andrew B., 2016. Movement: How the Brain Communicates with the World. *Cell*. Vol. 164, no. 6, pp. 1122–1135. ISSN 1097-4172. Available from DOI: 10.1016/j.cell.2016.02.038 (cit. on p. 36).

SHERMAN, Richard A.; SHERMAN, Crystal J.; PARKER, Laura, 1984. Chronic phantom and stump pain among American veterans: results of a survey. *Pain*. Vol. 18, no. 1, pp. 83–95. ISSN 0304-3959. Available from DOI: 10.1016/0304-3959(84)90128-3 (cit. on p. 20).

SHINODA, Y.; YOKOTA, J.; FUTAMI, T., 1981. Divergent projection of individual corticospinal axons to motoneurons of multiple muscles in the monkey. *Neuroscience Letters*. Vol. 23, no. 1, pp. 7–12. ISSN 0304-3940. Available from DOI: 10.1016/0304-3940(81)90182-8 (cit. on p. 28).

SMITH, Lauren H.; HARGROVE, Levi J., 2013. Comparison of surface and intramuscular EMG pattern recognition for simultaneous wrist/hand motion classification. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference* [online]. Vol. 2013, pp. 4223–4226 [visited on 2024-04-25]. ISSN 1557-170X. Available from DOI: 10.1109/EMBC.2013.6610477 (cit. on p. 66).

SUBRAMANIAN, Divya; ALERS, Anthony; SOMMER, Marc A., 2019. Corollary Discharge for Action and Cognition. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* [online]. Vol. 4, no. 9, pp. 782–790 [visited on 2024-06-06]. ISSN 24519022. Available from DOI: 10.1016/j.bpsc.2019.05.010 (cit. on p. 38).

TANIGUCHI, M.; CEDZICH, C.; SCHRAMM, J., 1993. Modification of cortical stimulation for motor evoked potentials under general anesthesia: technical description. *Neurosurgery*. Vol. 32, no. 2, pp. 219–226. ISSN 0148-396X. Available from DOI: 10.1227/00006123-199302000-00011 (cit. on p. 27).

TINAZZI, Michele; ZANETTE, Giampietro, 1998. Modulation of ipsilateral motor cortex in man during unimanual finger movements of different complexities. *Neuroscience Letters* [online]. Vol. 244, no. 3, pp. 121–124 [visited on 2024-10-22]. ISSN 03043940. Available from DOI: 10.1016/S0304-3940(98)00150-5 (cit. on p. 106).

TOUILLET, Amelie; PEULTIER-CELLI, Laetitia; NICOL, Caroline; JARRASSE, Nathanael; LOIRET, Isabelle; MARTINET, Noel; PAYSANT, Jean; DE GRAAF, Jozina, 2018. Characteristics of phantom upper limb mobility encourage phantom-mobility-based prosthesis control. *Scientific Reports* [online]. Vol. 8, no. 1, p. 15459 [visited on 2022-02-17]. ISSN 2045-2322. Available from DOI: 10.1038/s41598-018-33643-0. Number: 1 Publisher: Nature Publishing Group (cit. on pp. 13, 20–24, 45, 63, 64, 66–70, 78, 89, 91, 109).

WADE, Nicholas J., 2009. Beyond body experiences: Phantom limbs, pain and the locus of sensation. *Cortex* [online]. Vol. 45, no. 2, pp. 243–255 [visited on 2024-03-05]. ISSN 00109452. Available from DOI: 10.1016/j.cortex.2007.06.006 (cit. on pp. 18, 31).

WARD, Zina, 2014. Letter to the Editor: Reexamining Penfield's Homunculus. *Journal of the History of the Neurosciences* [online]. Vol. 23, no. 2, pp. 198–203 [visited on 2024-

03-22]. ISSN 0964-704X, ISSN 1744-5213. Available from DOI: 10.1080/0964704X.2013.868972 (cit. on p. 27).

WITHAM, Claire L.; RIDDLE, C. Nicholas; BAKER, Mark R.; BAKER, Stuart N., 2011. Contributions of descending and ascending pathways to corticomuscular coherence in humans. *Journal of Physiology*. Vol. 589, no. 15, pp. 3789–3800. ISSN 00223751. Available from DOI: 10.1113/jphysiol.2011.211045 (cit. on p. iv).

WITHAM, Claire L.; WANG, Minyan; BAKER, Stuart N., 2010. Corticomuscular coherence between motor cortex, somatosensory areas and forearm muscles in the monkey. *Frontiers in Systems Neuroscience*. Vol. 4, no. July, pp. 1–14. ISSN 16625137. Available from DOI: 10.3389/fnsys.2010.00038 (cit. on p. iv).

WOO, Shoshana L.; KUNG, Theodore A.; BROWN, David L.; LEONARD, James A.; KELLY, Brian M.; CEDERNA, Paul S., 2016. Regenerative Peripheral Nerve Interfaces for the Treatment of Postamputation Neuroma Pain: A Pilot Study. *Plastic and Reconstructive Surgery. Global Open*. Vol. 4, no. 12, e1038. ISSN 2169-7574. Available from DOI: 10.1097/GOX.0000000000001038 (cit. on p. 61).

WU, C. W.; KAAS, J. H., 2000. Spinal cord atrophy and reorganization of motoneuron connections following long-standing limb loss in primates. *Neuron*. Vol. 28, no. 3, pp. 967–978. ISSN 0896-6273. Available from DOI: 10.1016/s0896-6273(00)00167-7 (cit. on pp. 36, 41, 61, 69, 89).

XERRI, Christian; MERZENICH, Michael M.; PETERSON, Bret E.; JENKINS, William, 1998. Plasticity of Primary Somatosensory Cortex Paralleling Sensorimotor Skill Recovery From Stroke in Adult Monkeys. *Journal of Neurophysiology* [online]. Vol. 79, no. 4, pp. 2119–2148 [visited on 2024-09-13]. ISSN 0022-3077. Available from DOI: 10.1152/jn.1998.79.4.2119. Publisher: American Physiological Society (cit. on p. 30).

ZHANG, Yanlu; XIONG, Ye; MAHMOOD, Asim; MENG, Yuling; LIU, Zhongwu; QU, Changsheng; CHOPP, Michael, 2010. Sprouting of corticospinal tract axons from the contralateral hemisphere into the denervated side of the spinal cord is associated with functional recovery in adult rat after traumatic brain injury and erythropoietin treatment. *Brain Research*. Vol. 1353, pp. 249–257. ISSN 1872-6240. Available from DOI: 10.1016/j.brainres.2010.07.046 (cit. on pp. 14, 31).

A. Use of MEG to localize motor commands and somatosensory feedback of phantom hand movements

Our specific hypothesis regarding the sensorimotor loop underlying phantom hand movements in transhumeral amputees is that motor commands continue to originate from the the same pattenr of neurons in the motor cortex (schematically in the "hand area" but we have seen that somatotopy is limited in M1), indicating that the representation of the hand is preserved in M1. These motor commands are then transmitted to muscle effectors in the upper arm, as the original muscle effectors for intact hand movements (i.e., those in the hand and forearm) are no longer present. As discussed in previous chapters of this thesis, these muscle contractions in the residual upper arm are likely due, at least in part, to the fact that the remaining severed tissues have become the new targets of the severed nerves that formerly innervated more distal muscles. Consequently, according to our hypothesis, the somatosensory feedback would be processed both in the upper arm region and the hand region of the somatosensory cortex. Ths hypothesis is illustrated in Figure A.1

As developed in Chapter I however, during movement, the motor as well as the somatosensory cortices do not display a proper somatotopy in correspondance with the different subparts of the upper limb. Thus, it seemed difficult to precisely localize motor commands or somatosensory feedback of phantom hand movements without any reference point. In addition, natural dissimetry between hemispheres could render difficult the comparison between phantom and intact hand movements within the same participant but at the same time comparison between control participants and amputees might have added other confounding factors. Thus, we decided to compare the distance between the cortical sensorimotor representations of the phantom hand movement and the residual upper arm (i.e. the ontrol condition, taken as point of reference) with the distance between the sensorimotor representations of the intact hand and upper arm contralaterally in the same participant. This configuration likely ruled out any confounding factor previously cited. The task consisted in performing intact hand movements and contralateral phantom hand movements (hand opening and closing) alternatively. If our hypothesis is correct, the distances computed for motor commands in M1 should not differ significantly between the two sides, whereas the distances computed for somatosensory feedback in S1 should show a significant difference. This is because the area of activation during phantom hand movements is expected to encompass both the hand and arm regions, causing a lateral shift in the center of activity.

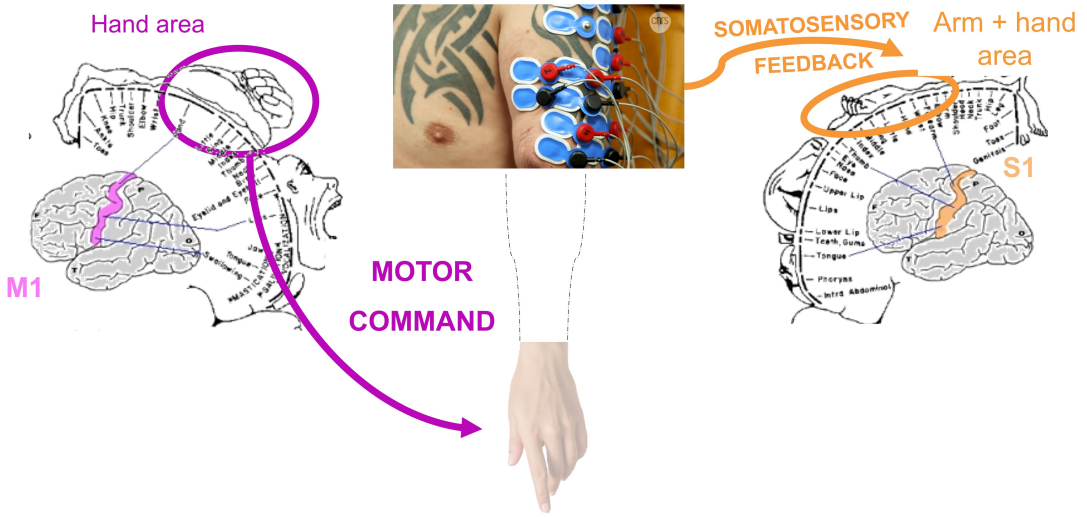

Figure A.1.: Hypothesis on the altered sensorimotor loop underlying phantom hand mobility. This hypothesis states that the motor commands remains similar after amputation which means that the hand representation in M1 is unaltered and taken schematically, they come from the hand area of M1. Because there is sprouting at the peripheral level, the new effectors are muscle subvolumes in the residual arm. Thus, the somatosensory feedback involves nerves that used to induce activation in the hand area of S1 but also probably the arm area. Because somatotopy in S1 and M1 during movement is not very clear, is is more rigorous to say that the somatosensory feedback activates more medial parts of S1 than it does during intact hand movements. This mismatch between motor commands and somatosensory feedback is thought to explain the phantom movement's difficulty of execution.

In this study, we had chosen to use magnetoencephalography (MEG), combined with a structural image of the brain (T1) as a recording tool. The idea was to take advantage of the high temporal resolution of MEG (in the order of 1 ms) in the hope to temporally separate the motor commands from the somatosensory feedback : around 20ms is needed for the motor commands to reach the muscles and the proprioceptive feedback of the movement reaches the cortex in additional 20 ms. The combination with the T1 image was chosen in order to be able to reconstruct the signal at the level of MEG sensors towards the level of brain sources to perform a precise 3D localization and take advantage of the high spatial resolution of MRI. EMG electrodes on the residual and intact upper arm muscles, as well as on one intrinsic muscle of the hand (FDI) were used to record muscle activity simultaneously. This choice was based on

previous litterature developping the metric called "corticomuscular coherence" in monkeys and humans during intact hand movements (Witham et al. 2010; Witham et al. 2011). In dynamic movements, coherence has been shown to exist between the cortex and the periphery in the gamma frequency range. The idea was to use this knowledge to localize the sensors that displayed the highest coherence value with the EMG signal recorded from intrinsic hand muscles or forearm muscles during intact movement. Then, once the result would reproduced for the intact condition, the idea was to explore the phantom condition.

We started to record from a control participant in order to prepare the pipeline of analysis. The pipeline of analysis was prepared with the FieldTrip Matlab Toolbox specifically built for EEG and MEG-based signal analysis. The pipeline was organized as follows :

1. Import MEG and EMG data
2. Use triggers to synchronize the two types of data
3. Preprocess both MEG and EMG data by filtering it and manually cut data into trials by using the right EMG channels as guides
4. Compute coherence metrics on preprocessed data.
5. Determine the best metrics and test ICA and reconstruction of MEG data at the source level using the T1 image, before computing the selected metrics.

There is extensive work behind this study, including the learning phase needed to master the toolbox and the notions of signal processing behind. Unfortunately, it could not be presented in a full chapter because, for various reasons developed in the following, no conclusive result could be extracted from it.

First, results previously reported in the literature (Witham et al. 2010; Witham et al. 2011) could not be reproduced on the intact side of the three amputees tested, nor on

the pilot control participant. After consulting with experts in coherence metrics, we slightly adapted the task to better align it with the one used in the literature. Instead of asking participants to perform self-paced movements without resistance, we imposed a movement frequency tailored to each participant, with the goal of maintaining consistency across trials. Additionally, to maximize the amplitude of EMG signals for proper analysis, participants were asked to perform hand-closing movements by squeezing a ball to provide resistance. The EMG signal amplitude was monitored using a MATLAB script I developed, which provided real-time visual feedback on the amplitude of the signal envelope. This ensured that the EMG signal was sufficiently strong for the coherence calculations. Unfortunately, these refinement of the task did not improve the results and we could not reproduce the results on the increase of signal amplitude in the gamma range of frequencies in the sensorimotor region, in spite of testing several techniques of analysis.

The reasons for this last failure are quite obscure. One lead to explain the fact that the results were not reproduced might be linked to the fact that the movements under study are dynamic movements while most studies that investigated cortico muscular coherence used a task where a position was maintained of the movement bas balistic with a high amplidue and short EMG signal. The quality of the data might also have been at cause because some sensors were out of order and the machine was old. Now that the lab is equiped with a brand new system based on Optically Pumped Magnetometers (OPM) it would be interesting to try to compute corticomuscular coherence using these types of signals.