THESIS FOR THE DEGREE OF LICENTIATE OF ENGINEERING

On the use of Phantom Motor Execution for the treatment of Phantom Limb Pain

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To Dalila

To the memories of Delfina, Eligio and Trudi

Abstract

Phantom limb pain (PLP) is a common complaint among amputees and despite having been studied for centuries, it remains a mysterious object of debate among researcher. To date, a vast number of ways to treat PLP has been proposed in the literature, however none of them has proven to be universally effective, thus creating uncertainty on how to operate clinically. The uncertainty is largely attributable to the scarcity of well conducted randomized controlled trials (RCTs) to prove the efficacy of PLP treatments.

Phantom Motor Execution (PME) -exertion of voluntary phantom limb movements – aims at restoring the control over the phantom limb and the exercise of such control has been hypothesized to reverse neural changes implicated in PLP. Preliminary evidence supporting this hypothesis has been provided by clinical investigations on upper limb amputees. The main purpose of this Licentiate thesis was to enable a RCT on the use of PME for the treatment of PLP in order to provide robust and unbiased evidence for clinical practice. However, the implementation and kick-off of this clinical investigation required to complete few preparatory steps. For example, most amputees and PLP patients have lower limb amputation, thus PME needed to be adapted and validated for this population. Further, the RCT protocol needed to be carefully planned and made openly accessible, as per guidelines for conducting and publishing clinical RCT. Finally, a secondary aim of this thesis emerged with the need of providing long term relief from PLP to patient. Preliminary evidence seemed to indicate that in order to maintain pain relief, periodic rehearsal of the phantom motor skills acquired through PME is necessary. This raised the question of whether it is beneficial and possible to translate the technology from clinic to home use, question that was explored employing both quantitative and qualitative methods from engineering, medical anthropology, and user interface design.

The work conducted within this thesis resulted in the extension of PME to lower limb patients by proposal and validation of a new and more user-friendly recording configuration to record EMG signals. The use of PME was then shown to be efficacious in relieving PLP with a case study on a patient. The protocol for the RCT was then designed and published. These two first steps permitted the establishment of the RCT, which is currently ongoing and expected to close in March 2021. With regard to the secondary aim of this thesis, the work conducted enabled PME to be used by the patients in the comfort of their home, while it also allowed investigate the benefits and challenges generally faced (not only by PME) in the transition from the clinic to home and its effects on treatment adherence. The work conducted is presented in the three appended publications.

Future work includes the presentation of the results of the RCT. Further, having a way to modulate PLP is an incredibly useful tool to study the neural basis of PLP. By capitalizing on this tool, we are currently conducting brain imaging studies using fMRI and electroencephalography that are the main focus of the work that lies ahead.

Keywords: Phantom Limb Pain, Phantom Limb Sensations, Phantom Motor Execution, Amputation, Randomized Controlled Clinical Trial.

List of Publications

This thesis is based on the following publications:

[A] **Lendaro E**, Mastinu E, Håkansson B, Ortiz-Catalan M. Real-time classification of non-weight bearing lower-limb movements using EMG to facilitate phantom motor execution: Engineering and case study application on phantom limb pain, *Published in Frontiers in Neurology, 2017,8(SEP):1-12*

[B] **Lendaro E**, Hermansson L, Burger H, et al. Phantom motor execution as a treatment for phantom limb pain: protocol of an international, double-blind, randomised controlled clinical trial, *Published in British Medical Journal Open, 2018;8(7):e021039.*

[C] **Lendaro E**, Middleton A, Brown S, Ortiz-Catalan M. Out of the Clinic, into the Home: The in-Home Use of Phantom Motor Execution Aided by Machine Learning and Augmented Reality for the Treatment of Phantom Limb Pain, *Published in Journal of Pain Research, 2020;13:195-209.*

Other publications by the author, not included in this thesis, are:

Lendaro E, and Ortiz-Catalan M, "Classification of Non-Weight Bearing Lower Limb Movements: Towards a Potential Treatment for Phantom Limb Pain Based on Myoelectric Pattern Recognition", Published in *Proceedings of the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2016:.5457-5460.*

Lendaro E, Nilsson S, and Ortiz-Catalan M, "Differential Activation of Biceps Brachii Muscle Compartments for Human-Machine Interfacing", Published in *Proceedings of the 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2018: 4705-4709.*

Mastinu E, Ahlberg J, **Lendaro E**, Hermansson L, Hakansson B, Ortiz-Catalan M. An Alternative Myoelectric Pattern Recognition Approach for the Control of Hand Prostheses: A Case Study of Use in Daily Life by a Dysmelia Subject., Published in *IEEE Journal of Translational Engineering in Health and Medicine*, 2018;6: 1-12.

Lendaro E, Guo L, Novoa MJM, Sandsjö L, Ortiz-Catalan M "Seamless Integrated Textrode-Band for Real-time Lower Limb Movements Classification to Facilitate Self-Administrated Phantom Limb Pain Treatment", Published in *Proceedings of the 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2019: 1753-1756.*

Acronyms

PLS:	Phantom Limb Sensations
PLP:	Phantom Limb Pain
RLP:	Residual Limb Pain
MPQ:	McGill Pain Questionnaire
PNS:	Peripheral Nervous System
PME:	Phantom Motor Execution
CNS:	Central Nervous System
S1:	Primary Somatosensory Cortex
S2:	Secondary Somatosensory Cortex
M1:	Primary Motor Cortex
SM1	Primary Somatosensory Cortex
RCT:	Randomized Controlled Trial
fMRI:	Functional Magnetic Resonance Imaging
MPR:	Myoelectric Pattern Recognition
EMG:	Electromyogram

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For the friends I met during the leadership program. It seems almost impossible to be able to find a group with so many inspiring people that want to make the world a better place. And yet it happened, and they are my friends. Stay hungry!

For my family and dear friends (you know who you are). They are the strong roots that made me able to endure storms. Un grazie speciale a te, papá: questa tesi é stata condotta secondo il tuo stile di ottimizzazione degli ultimi minuti. Non mi hai mai insegnato questa tecnica, é passata dai geni :)

For S90, V90 and Gimmy: happiness is real only when shared. Thank you for making it real. And thank you for loving me unconditionally. 你永远是我的企鹅!

Contents

Part I

Overview

CHAPTER 1

Introduction

Motivation

Phantom limb pain (PLP) — "painful sensations referred to the lost body part"[1] — is a common complaint among amputees, with different sources attesting its prevalence between 50% and 88% [2]. As other chronic neuropathic pain conditions, PLP has negative effects on a person's well-being. For example, amputees with PLP are less likely to wear a prosthesis thus resulting in additional disability [3]. Moreover, most amputees report PLP to affect their sleep and episodes can be so intense to wake the sufferers through the night [4]. This causes the sufferer to be sleep deprived, condition which has been shown to reduce pain tolerance [5]. PLP can also have social implications. For examples, it has been shown that PLP decrease employment and satisfaction with working life [6]. Despite being a known condition since a long time, first appearing in the literature in 1551 [7], PLP is still poorly understood. Signs of this lack of understanding are for instance the fact that despite the large number of treatments described in the literature, none of them has proven to be decisively effective and guidelines for treating patients are currently absent [8]. This can be largely attributed to the scarcity of Randomized Controlled Trials (RCTs) on such treatments, which additionally tend to be of poor quality [9]. More recently, restoration of the control over the phantom limb and the exercise of such control have been hypothesized to reverse neural changes implicated in PLP [10]–[12] and preliminary evidence in support of this hypothesis has been provided by clinical investigations on upper limb amputees [13], [14]. The approach to enable phantom motor execution (PME) is based on the use of a myoelectric pattern recognition (MPR) system that allows to decode motor volition while providing real-time feedback via virtual and augmented reality (VR-AR). Exercising PME is hypothesized to reengage the motor neural circuitry in the central and peripheral nervous systems, ultimately resulting in PLP reduction. However, the evidence in support of PME as an effective way to treat PLP was obtained only on upper limb amputees at first. Further these clinical investigations were not conducted as RCTs. Hence, they did not ensure that the effects on pain relief reported were not due to any factor other than the active treatment component (i.e. PME).

When considering how the reduction of PLP relates to acquisition and maintenance of motor skills of the phantom limb, it becomes clear that PME is not a cure for PLP which can be taken at one instance and solve the problem forever. The preliminary evidence available seems to indicate that in order to maintain pain relief, periodic rehearsal of the phantom motor skills acquired through PME is necessary. PME should therefore be regarded as a habitual practice to maintain skilled control over the phantom

limb. The question as to whether this treatment approach could be self-administered at home and what would be required in order to ensure treatment quality and adherence then emerges naturally.

Finally, having access to a proved method of relieving patients from PLP would not only be important for improving the life of those suffering from it, but it would also be very useful to increase our understanding of the neural basis of this curious phenomenon. For example, an efficacious treatment would allow to modulate PLP and to study the neural correlates of such modulation. Phantom sensations (painful and non) are a peculiar phenomenon that raises a host of challenging questions relevant to philosophy, psychology, and neuroscience. The following quotation of. Joel Katz during an interview with Cassandra Crawford [15], clearly summarizes what researchers find fascinating in the experience of phantom limbs-

"I think that whoever solves the puzzle or problem of the phantom limb will also solve the problem of perception . . .That is what I like so much about the phantom: I think of it as a window into the central nervous system"

Katz 2005

Scope

This licentiate thesis is focused on the following tasks:

1. Technologically enabling PME by use of MPR and VR/AR in lower limb amputation (Paper A).
2. Providing evidence that PME is a viable option for PLP relief in lower limb amputees (Paper A).
3. Design a large-scale, international RCT in order to gather unbiased and stronger evidence of PME as a valid treatment for PLP (Paper B).
4. Enabling patients to use PME aided by MPR and VR/AR at home and monitor the progression of their PLP (Paper C).

Thesis outline

This thesis is divided in two parts. Part I is constituted by eight introductory chapters, including the present one, that intend to give an overview of the research field and the reasons that motivated this work. Chapter 2 describes the historical context, the major contributors to the field and the prevailing neuroscientific theories that have provided the boundaries for what phantom limbs can be or can do from a theoretical perspective. Chapter 3 describes the experience of phantom phenomena from a phenomenological perspective. Chapter 4 seeks to give a neurological explanation of phantom limb sensations (PLS) and PLP giving an overview of the central and peripheral mechanisms involved. Chapter 5 lays out an overview on the prevailing theories of PLP and PLS. Chapter 6 gives an overview of the currently available treatments, giving special attention to PME. Chapter 6 provides a summary of the contributions of the included papers. Finally, Chapter 7 outlines of the work ahead. Part II contains the appended publications of this thesis.

CHAPTER 2

Historical Context

Amputation is one of the most serious surgical interventions and the thought that early societies, which we often call "primitive", were able to perform it successfully is fascinating. We find evidence of this in 27,000-years old cave paintings showing the imprint of hands with missing phalanges (**Figure 1**) [16], or in the oldest successful trans-humeral amputation found in a Neolithic site (4900-4700 BC) in France [17]. Moreover, survival after amputation is also well documented throughout history as abundant archeologic findings of prosthetics devices can confirm [18], [19]. Yet, perhaps even more fascinating is the total absence of phantom limbs from medical records until the 16th century: quoting Prince and Twombly "there is every reason to suppose, and no reason to doubt, that individuals with an amputation have, in all times, experienced phantom sensations of some kind . . ."[20]. These observations rise the question of why certain phenomena are reported in medical literature while others remain unnoticed. For instance, one could legitimately wonder how come migraine was already known by the Ancient Egyptians (2500 BC) [21], whereas phantom pain was never mentioned before 1551, the year when Paré (1510–1590) made the first documented reference [22]. Following up on this thought, one could also be intrigued by the fact that, starting from that first report onwards, phantom limbs became a topic of high scientific interest to the point that the literature available today has past reached forbidding proportions.

Figure 1: Negative hands*. Impressions of hands made by stencil technique from the Upper Paleolithic period (about 27,000 years old). The paintings are found in the Caves of Gargas in the Pyrenees region of France.*

One interpretation is to regard this as an example of how the scientific and medical community may not be open to investigation of a sensorial phenomenon, unless it can be integrated in the body of theories of the time. This implies that the very first accounts might have provided a paranormal interpretation of the perceptual experience instead of a scientific

one. For example, while examining medieval folklore accounts describing the loss and miraculous restoration of body parts, Price and Twombly [20] came across what they judged to be clear metaphorical allusions to phantom limb phenomena, thus pushing back the recorded history of phantom limbs to the tenth century. In his historical account of the process that brought phantom limbs from being a miraculous phenomenon to an instrument for investigating neural plasticity and consciousness, Wade [23] ascribes these early folkloristic descriptions to the first phase of the process. It is only in later phases that descriptions are furnished with theoretical speculations. Noteworthy is Finger and Hustwit's work [24] where they addressed the history of phantom limbs by reviewing the contributions made to the medical literature before the 20th century, thus giving an insight of how many people from a variety of different back-grounds were writing on the topic, each with different motives in mind.

Paré (1510) provided the first of report of phantom limbs to the medical field. He was a French military surgeon that made considerable progresses in the surgical amputation technique in a time when the most common cause for this intervention was gangrene [23]. As a result of his improved technique, patients were now more likely to survive, which led him to work more closely with amputees. For instance, he designed several ingenious prostheses with movable parts (**Figure 2**). Through his work with amputees, he also discovered that they tended to have sensations in their lost limbs. In line with his primary purpose of improving the surgical procedure for amputation, he eventually wrote a commentary warning to other surgeons of the existence of deceptive sensations (phantom sensations) in dead tissue which may dissuade from performing a lifesaving amputation required to stop the gangrene from spreading [24].

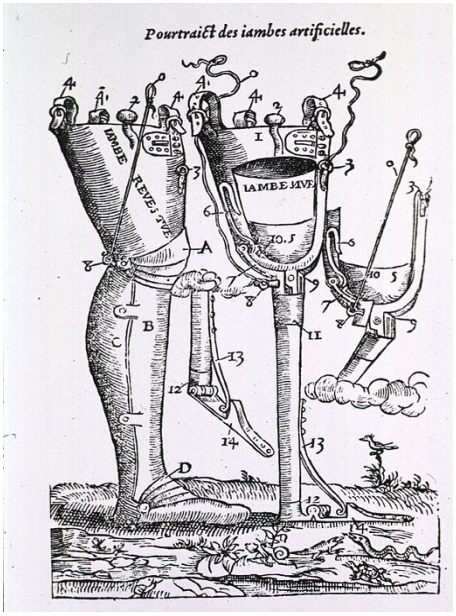

***Figure 2: Artificial leg**. Leg designed by Ambroise Paré (1575) available in the collection of Images from the History of Medicine, which is a library of the U.S. government's National Institutes of Health, Public Domain.*

By ascribing the phantom feelings to the stimulation of the severed stump nerves, Paré's initial accounts were integrated with the prevailing theory of perception of his time [25]. In contrast, just few decades later, Descartes decided to take his theoretical speculations beyond the commonplace knowledge of his time and exploited the phenomenon to corroborate his dualistic philosophy of body and mind, specifically as a proof of the fragmented and unreliable nature of the senses and as a further evidence of the unity of the mind. These two first reports remained rather isolated until the nineteenth century when also other scientists incorporated phantom limbs into their work. Reasonably this incorporation process was catalyzed by the establishment of basic neuroscientific concepts such as the existence of nerve cells and animal electricity [26], the law of specific nerve energies (Muller [27]), the idea of pain as an independent tactile quality

(Frey [27]), or the existence of a sixth sense associated with the muscles (Bell [28]). Further, it was during this period that Silas Weir Mitchell (1829–1914) [29], one of the founders of neurology in the United States, coined the name “phantom limb” unequivocally introducing the concept in the scientific discourse.

Throughout the nineteenth century most views on the mechanisms underlying phantom sensations converged on the general idea that activity in the severed nerves alone could account for the manifestation of phantoms [30]. However, with the turn of the twentieth century and the rise of neurology, the peripheral theory started to be challenged by a dichotomous central interpretation, in which the central nervous system came to assume the primary role. Precisely, this view can be traced back to the early 1900s when Head and Holmes (1911) coined the concept of “body schema” to describe the spatial model of the body that the brain constructs based on sensory inputs. Building on this, Pick (1915) proposed that phantom phenomena are perceptual manifestations of the persistence of the lost limb in the body schema [31]. In accordance with this view, he also remarked that children with congenital absence of limbs, or after amputation in the first years of life, do not have phantom limbs due to the lack of afference required to build the body schema.

Two decades after Head and Holmes, Schilder (1935) began what Crawford renamed as the psychologization of the body schema. Namely, he deemed that the emotional processes are necessary in order to guide the sensations and perceptions that form the body schema [15]. Within this framework, the phantom represented “a reactivation of a given perceptive pattern by emotional forces” [32]. This view, combined with the concept of denial in psychology, popularized by Anna Freud, eventually led to psychogenic explanations of phantom pain such as the view of pain as the narcissistic inability to renounce the integrity of the body and adapt to the defect [15][33]. In clinical practice, psychogenic explanations tended to convene to the conclusion that phantom pain is the interpretation of phantom sensations by individuals who show psychopathology [34].

The notion of phantom limbs as expression of psychological trouble remained unchallenged till post second world war, however further advances in neurology created favorable conditions for a shift. In particular, the cortical homunculus (**Figure 3**), discovered by Wilder Penfield and colleagues in 1937 [35], is the key concept that allowed phantom limbs to take official residence in the cerebral cortex of amputees. Early references to Penfield’s homunculus were in line with the body schema theory and regarded the somatic and motor cortical maps as the physical manifestation of it. Subsequently the homunculus was used to account for the morphology and certain phenomenological peculiarities of phantom limbs. For example, it was used to explain why sensations in extremities, such as phantom hands or feet, tended to be more vivid than those arising from other parts. Namely, most vivid phantom sensations were said to be perceived in those body areas with the largest cortical

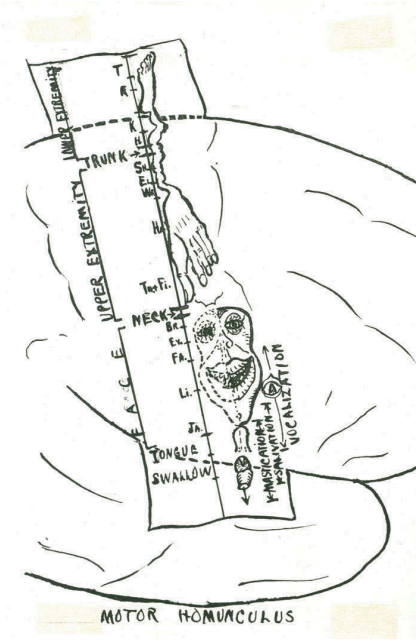

Figure 3: The motor homunculus. *Sketch by Penfield, probably 1951. ©Osler Library of the History of Medicine.*

representations. Similarly, telescoping -the perception of a shortening phantom- and the fading out of parts such as forearms and shins of the phantom was seen as a consequent of the fact that those portion of the phantom were less vivid to start with [36]. In this light, the fact that phantom experiences in people with congenital limb absence were not reported until 1961 [37] does not surprise. As already mentioned, phantom sensations in congenital limb absence were irreconcilable with the early body schema theories. Indeed, congenital sensations were explicable only by admitting that the body schema was at least partly built in the central nervous system. Melzack later commented that previous reports of phantom experience in congenital amputees were probably rejected due to the lack of conceptual framework to make sense of these accounts [38].

Although the idea of an innate neurophysiological structure of the phantom was first provided by Penfield's work in 1937 it was not until the 1990s, also thanks to extensive foundation work conducted during the 1980s on monkeys [39]–[45], that the homunculus was used to provide empirical evidence of the properties of these maps in relation to phantom sensations. The microelectrode mapping done on monkeys investigated the effect of deafferentation and amputation on cortical sensorimotor maps and came to challenge the idea that the adult brain is hardwired with stable neuronal connections.

By the mid-90s, thanks to the advance of medical imaging technologies, it became possible to examine whether adult plasticity takes place also in humans and to further study the perceptual correlates of such plasticity, which could not be done in animals. This led to phantom phenomena being attributed to plastic changes in the cortex taking place after amputation. For example, cases of phantom referred sensations prompted by far-removed trigger points, previously unexplainable by peripheral theories and by fixed neural connections, started to be documented only now. This type of sensations is also known as "dual percept" because it is perceived as if it were applied simultaneously at the actual stimulation point and at a location on the missing limb [46]. Perhaps the most known report of this dual percept phenomenon comes from Ramachandran and others [47]–[50] demonstrating that referred sensations are evoked in phantom limbs by stimulating topographically organized hand maps in the lower face and stump. They explained the referral of sensations as a result of cortical plasticity where face and stump representations invade the deafferented area, as corroborated by the layout of Penfield's homunculus were the hand area is flanked by the face representation on one side and the wrist's on the other. They further suggested that this remapping could explain the very existence of phantom limbs:

spurious discharges from neurons innervating the trigger zones could be interpreted as originating from the missing limb. It was later pointed out that this phenomenon is actually exceptionally rare (present in <7% of the cases) [51] and therefore could not explain the presence of phantom phenomena, which are virtually universal in amputees. Moreover, it has been shown that the topography of referred sensation is rather dynamic over time while the invasion into the deafferented cortical zones was said to be a very robust phenomenon [52].

Throughout the last two decades the discourse has mostly focused on determining the nature of the cortical reorganization taking place after deafferentation and its implications for phantom phenomena. Elbert and Rockstroh (2004) outlined the range of reorganizational changes taking place in the human representational cortex and identified three distinct modalities. Namely "experience- or use-dependent" plasticity, enhanced by behaviorally relevant afferent activity; "injury-related" reorganization, driven by loss of input as in the case of amputation or blindness, and "maladaptive" plasticity, as in the case of focal hand dystonia that causes involuntary movement or cramps and is triggered by intensive training of a particular movement [53]. In the recent years, these plasticity models have been used and disputed by different research groups to explain the etiology of PLP. On one side a maladaptive plasticity interpretation sees PLP as the perceptual correlate of maladaptive reorganization [54], on the other side an experience-dependent plasticity interpretation regards phantom pain as the driving force that preserves the representation of the missing limb [55]. Non-painful phantom sensations have been investigated to a lesser extent also owing to the difficulty of reliably evoking these sensations, however it has been shown that phantoms sensations are not related to cortical reorganization [51], [56]. Another undeniable source of cortical change is the use-dependent plasticity resulting from the use of a prosthesis or the adaptive compensatory use of other body parts [57], [58]. These effects should also be taken into account when looking for a neural correlate of phantom phenomena. The debate is far from being settled, leaving open the question of how of phantom limbs and phantom pain originate and become chronic. Phantom limbs have a special place in neuroscience: not only can they serve as markers for tracking neural plasticity in the adult brain, but they can also provide fundamental insights into the processes underlying bodily awareness and consciousness.

The purpose of this chapter was to give an historical context to the biography of phantom limbs and pain. This should provide a sense of how tightly linked the etiology and manifestation of phantoms limbs are to what is considered legitimate by the current theoretical framework. As we have seen, the context seems to set the limits of what is possible for phantom limbs to be, feel and do. The following chapter is dedicated to the phenomenology of phantom limbs, however in the light of what has just been pointed out, I encourage to read what follows keeping in mind that although the literature has exploded in size, and the characteristics of phantom limbs have already been investigated far and wide, the story we are telling probably remains incomplete.

"Normal science does not aim at novelties of fact or theory and, when successful, finds none"

Thomas Kuhn

CHAPTER 3

Phenomenology of phantom limbs

The purpose of this chapter is to provide a description of the experience of phantom phenomena. It must be noted that this is an incredibly challenging task since the study of phantom limbs is tightly linked to the study of the content of conscious experience, such as perceptions, feelings and emotions, which is subjective. The difficulty of establishing an objective description is reflected in the contradictory accounts found throughout the literature which are largely based on short-term studies with small groups or exceptional cases. This chapter is concerned with the phenomenology of phantom limbs, which focuses on determining the essential properties of this experience rather than giving a psychological or neurological description.

A common and natural consequence of amputation is the perception of phantom phenomena: the perception of sensations located in a missing limb [59]. Phantoms have also been reported occurring following mastectomy [60], [61], amputation of genitals [62], rectum [63], and removal of other body parts such as eyes [64], bladder [65], uterus [66], tongues [67], or teeth [68]. Moreover, phantom phenomena are also associated with conditions other than amputation. This is the case for supernumerary phantom limbs occurring following nerve avulsion [69], spinal cord injury [70], stroke [71], head injurie [72], anesthetic nerve block [73]. Further, it has been found that phantom limbs were experienced also by about 20% of children with congenital limb absence [37], [38].

Phantoms limb can be perceived with the vividness of a real limb. For example, it has long been documented how amputees may forget the loss of the limb and reflexively attempt to step out of bed, answer the phone, rub an eye, or shake hands with the missing limb [74]. The remarkable reality of phantom limbs owes to the wide range of sensations experienced, which can be non-painful or painful. Another common consequence of amputation is the perception of pain in the residual limb, which is called stump pain or residual limb pain (RLP). Non-painful phantom sensations do not pose a clinical problem for the amputee however they often coexist with RLS and phantom pain and oftentimes influence each other [75], resulting in additional difficulty to separate these elements for appropriate treatment.

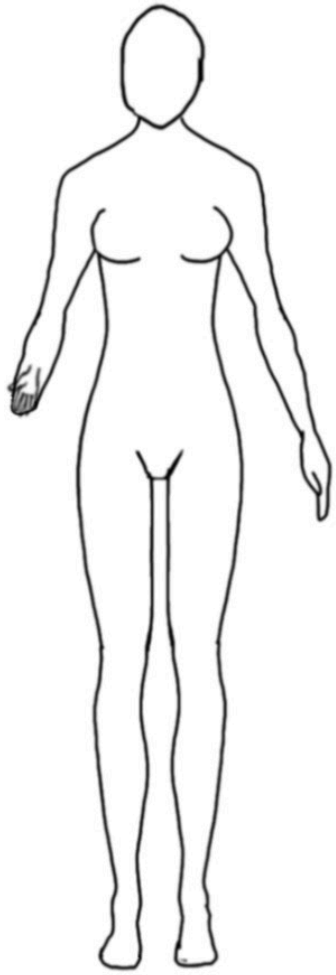

***Figure 4: Telescoping**. Patient with phantom retracted into her stump.*

In order to disambiguate the descriptions of phantom phenomena, Danke [76] introduced a taxonomy, later popularized by Nikolajsen and Jensen [2] as the "phantom complex". Components of the phantom complex are phantom limb pain (PLP) - painful sensations referred to the absent limb; phantom limb sensation (PLS) - any sensation in the absent limb, except pain; and stump or residual limb pain (RLP) - pain localized in the stump. However, more recently it has emerged that this definition is problematic as it is based on the perceived location of the pain and it fails to acknowledge the multiple etiologies behind RLP, such as neuroma, complex regional pain syndrome, and nociceptive pathology [77], [78]. The main problem with grouping different pathophysiological mechanisms under the common label of RLP is the risk of not recognizing that neuroma pain (NP) can manifest itself as pain in the missing limb [79], [80], and thus be classified as PLP without actually being such. Another problem relative to the categorization of postamputation pain based on the perceived location, is the fact that phantoms limbs are sometimes perceived within the residual limb (Figure 4) [81]–[83]. In order to correctly classify the pain, which is essential for proper treatment, it is therefore necessary to consider the pathophysiology of the pain reported by the patient. The purpose of the rest of this chapter is to describe the phenomenology of phantom sensations and phantom pain. A general description of the various types of RLP together with a more detailed description of their pathophysiology is given in Chapter 4.

Phantom sensations

The prevalence (not to be confused with incidence) of non-painful sensations has been reported in 70% to virtually all acquired amputees [48], [84]–[88]. Importantly, Hunter *et al.* recognized that phantom limb awareness, the general awareness of the existence of the missing body part, is a distinct trait of phantom limbs which is qualitatively different from the experience of specific nonpainful somatic sensations [46]. Weinstein recognized three types of PLS, namely exteroceptive, kinesthetic and kinetic sensations [89].

Exteroceptive sensations include a wide range of sensory aspects, such as tingling, itching, pressure, warmth, or cold [46], and super-added phantom features, such as the sensation of wearing a shoe, a watch, or a glove [90].

Phantom limbs are inherently endowed with proprioception and corporal awareness (kinaesthetic sensations): they are perceived to occupy a plausible body space, usually aligning with the stump and moving with it [91], and are perceived to be of a particular size, shape and

posture [92]. For example, phantoms may feel perfectly normal in all respects, retaining a shape and form of the former limbs [86], [93], however with time they may also fade away leaving the phantom with missing parts [69]. In some cases phantom limbs can be in an habitual and normal position, conversely they might also occupy an abnormal position which can be constantly fixed or anatomically impossible [87][48]. Phantom can be weightless or be perceived as heavier than normal limbs [86], and often they are reported to shrink in size or shorten in length in a process first described by Guéniot in 1861 [96] and known as telescoping. Nevertheless, telescoped phantoms can also grow back and return to their full length, for instance when wearing a prosthesis (**Figure 5**) [95]. Likewise, they can actively telescope back when doffing the prosthesis [87]. Amputees tend to perceive predominantly the distal parts of the limb, although perception of exclusively proximal portions is also possible [87].The perception of distal parts of the phantom, in combination with the dropping out of the proximal parts leads to the perception of the phantom as detached from the residual limb, floating in air (**Figure 6**) [70].

Finally, amputees can perceive kinetic sensations, of voluntary or involuntary movements [97]. Ramachandran and Altschuler [98] reported that many patients can voluntarily move their phantoms, but they also reported an equal number of amputees that claimed that their phantom is immobile, assimilating this kind of paralysis to the “learned paralysis” that commonly affects stroke patients. Controllable phantoms have been described as intentionally exploitable, as illustrated by Poeck (1964) with the example of an 11-year old girl with bilateral peromelia who learned to solve simple arithmetic problems by counting on her phantom fingers [99]. Another famous example is provided by pianist Paul Wittgenstein, whose right arm was amputated during WWII. After the war he learned to play the piano with his left hand resuming his concert pianist career. It is believed that the movements of his phantom hand played a crucial role in the acquisition of his unusual left-handed dexterity, as he allegedly used the phantom hand to choose how to use the fingers for pressing the piano keys [100]. Spontaneous movements are instead exemplified by Fairley’s patient who remarked, “When I play tennis, my phantom will do what it’s supposed to do… It will give me balance in hard shots”. Involuntary and automatic phantom movements have been described as jerking, jolting, spasm or tremor movements [101]. An example of these is provided by McGrath and Hiller’s patient who experienced an unusual sensation referred to as nerves jumping, which was described as a “weird tingling that starts in your toes and goes up to your stump and the nerves jump. The stump jumps up and down (1 or 2 inches) for a few seconds.”[102].

It has also been reported that phantom limbs interact with the surrounding world and have different adaptation strategies. The most exhaustive study in this regard was authored by Jalavisto [103]. In this study, 173 subjects were asked to give an accurate account of what happens to their phantom when they are placed near a wall or table and had to move the stump so that the phantom, if unchanged, would occupy some place within the wall or the table. Two main strategies for phantom-object interaction emerged, namely an adaptive strategy, in which the phantom disappears, shuns the obstacle or moves, and a fixed strategy in which the phantoms do not adapt and penetrate objects instead. Interestingly, it was found

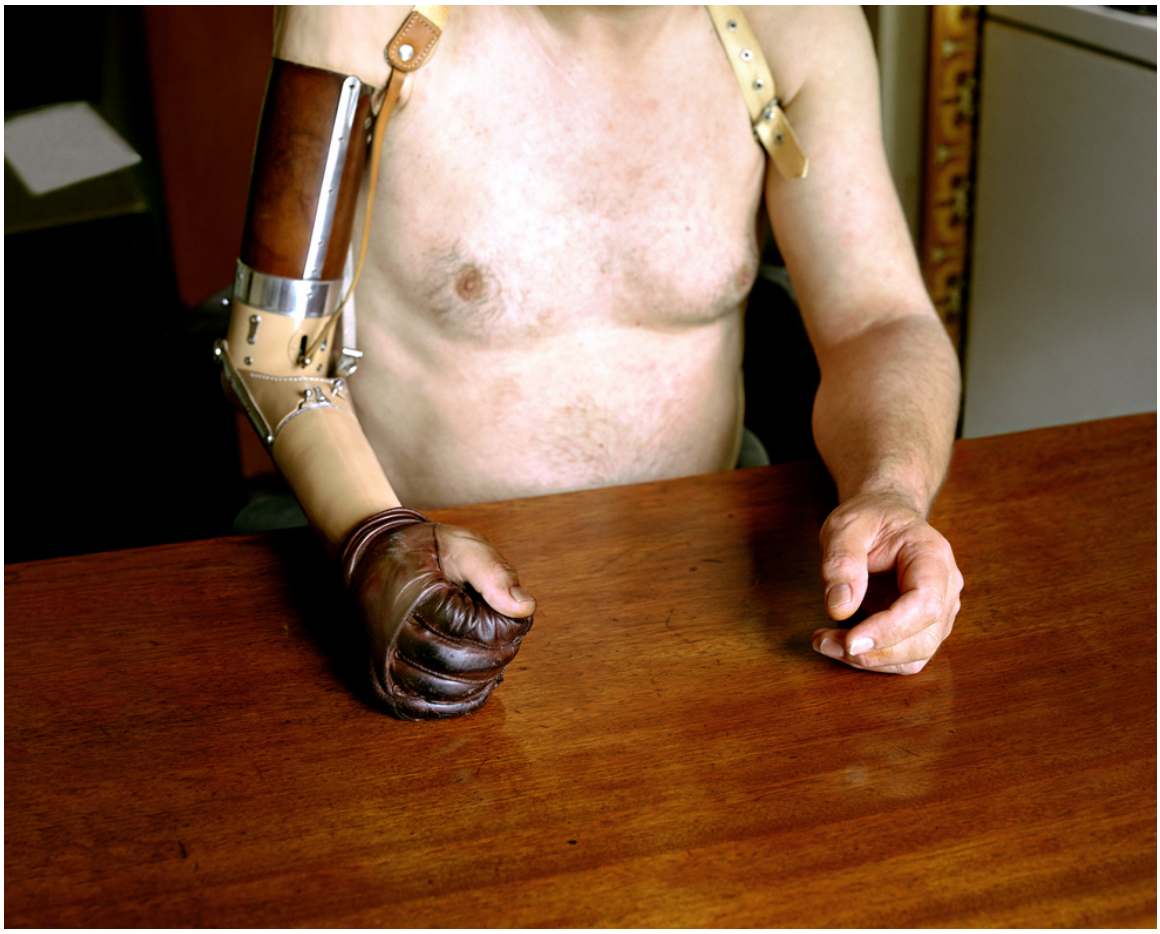

Figure 5: After Image GN2.
(Caption and photo reprinted with permission from Wright, Alexa. 1997. After Image. London, England: www.alexawright.com.)

GN
Date of amputation: 1964
Time since amputation: 33 years
Age: 52 Male
Motor cycle accident: brachial plexus lesion
Arm amputated 4 months after accident
No previous damage to limb

"At first I had a phantom limb whilst the arm was still there, because the arm was paralyzed. The phantom used to float away from where the arm was. I was in a hospital bed and it would float through the bedclothes and get cold, so I developed this habit of sleeping on my right side so the phantom limb drifted into the mattress and stayed warm. At the beginning used to believe I could get the arm back.
Now nearly all of the arm has disappeared, but if I am wearing the artificial arm and I swing my arms as I walk, the right arm swings. If I can see the artificial hand out of the corner of my eye or I can feel it up against my leg the phantom hand is inside the glove. If I can't see the artificial hand, I can be wrong; I could be six inches out as to the location of the hand: the phantom hand can miss the artificial one in terms of spatial placing.
There is an intermittent crushing pain, but the phantom is always there. It's part of me; it will never go away completely. I will always be this; I will always have two arms, it's just that one of them is missing. The real me is without the prosthesis; its uncomfortable; it's not me. It is surprising how one armed I look when I see photographs of myself; my self-image is two armed."

Figure 6: After Image RD2
(Caption and photo reprinted with permission from Wright, Alexa. 1997. After Image. London, England: www.alexawright.com.)

Date of amputation: October 1995
Time post amputation: 21 months
Age 71: Male
Road accident in which arm was crushed
No previous damage to arm

"As our car bowled over in collision with another car, my arm went out of the window and was crushed. X-rays later revealed that the arm was severely damaged, but the hand was left intact.
The phantom is continuous; it takes the form of my hand. It is sometimes painful and sometimes just sensation. I feel I can control the movements of the hand until I suddenly realize that it isn't there. The hand is slightly clenched fist, and that doesn't really change; it can only go about three quarters unclenched. The pain is mostly in the third finger; that sometimes hurts and is painful as though I had broken it. The hand is the same size as my real hand, but much heavier. It itches a lot of the time and I want to scratch it.
I can kid myself that I can make the phantom limb move. It's really just a sort of opening & closing: the hand moves from the wrist downwards, but rotation of the wrist isn't available. I have only got finger and hand joint movements. When I haven't moved it for a while it becomes stiff.
I can't imagine being without the phantom because it is there all the time and it is very much like eating or breathing: I can put up with it quite adequately and would probably miss it if it went away. I might wish it wasn't so irritating, but I think I would rather keep it as it is than risk losing it."

that that amputees younger than twenty-five were more likely to described their phantoms as disappearing or moving when approaching the obstacle (adaptive phantoms), while amputees over age twenty-five tended to describe their phantoms as passing into the wall (fixed phantoms) [103].

The temporal characteristics of phantom limbs are remarkably variable. Among the people experiencing PLS, the vast majority reports of being aware of PLS within the first week post amputation, while the reminder perceives them within the first few weeks [86][88]. Some patients experience the missing limb for only a few days or weeks, while others, an estimated 30%, continue to experience it for decades [104]. Finally, the PLS can be spontaneous (independent from any kind of stimulus) or they can be stimulus-dependent (i.e. evoked) by a discrete event or condition [105], [106].

Giummarra *et al.* [87] points out that one of the limitations of the literature of PLS is the anecdotal or incomplete nature of the descriptions that only explore isolated features of the phantom or are based on small sample sizes and extraordinary cases. To overcome this shortfall they ran a systematic phenomenological study on 283 amputees reporting the prevalence of for each of the various features of PLS, together with related protective and/or risk factors emerged from the analysis. **Table 1** reports a summary of the number of participants who perceived a specific PLS. The authors found that telescoping was more common among upper limb amputees and amputees with more proximal amputations (both upper and lower limbs). Telescoping was instead less common among amputees who underwent vascular or diabetic amputation. The size of the phantom was not influenced by amputation level; however, the size is perceived more clearly when pain was also present. Participants reporting anatomically impossible postures were more likely to be traumatic amputees, while normal posture was more common in those patients with some form of functional impairment prior amputation. More proximal amputation resulted in phantoms with more varied positions. No differences in exteroception and proprioception of phantom limb was found considering cause of limb loss, functional impairment prior to amputation, infection or gangrene prior to amputation. Upper limbs were however more likely to report temperature in their phantom limbs. Finally, prosthesis embodiment was more frequent in amputees with an extended phantom compared to a telescoped phantom [87].

Phantom limb pain

PLP has been long described in the literature however the many accounts are often inconsistent and contradict each other, leaving the newcomer to the field amidst confusion. The contradiction starts when trying to determine the mere prevalence of the condition. Early reports were more contradictory, with some indicating very low prevalence rates of PLP (1-5%) [33], [34], [36], [107] and others as high as 50% [91]. Recent reports are more homogeneous reporting rates between 60% and 80% [15], [108],[109]. **Table 2** is taken from Crawford's book "Phantom limb: Amputation, embodiment, and prosthetic technology" (2015) [15] and shows how the prevalence of PLP has steadily increased over the years up until the 90s, then reducing slightly with the turn of the twenty-first century. The large discrepancies and low

Table 1 :Prevalence of Phantom Limb Sensations*. Summary of the results of the survey conducted by Giummarra et al. [87]. The table reports the number (per cent) of participants of the study who perceived a phantom limb with various sensation.*

	N (%)
Phantom limb perception and pain	
Non-painful phantom limb sensations (PLS)	207 (73.1)
Phantom limb pain (PLP)	191 (67.5)
PLP and PLS (partially overlapping data above)	135 (47.7)
Frequency of PLS at present	
Constantly	102 (35)
A few times an hour	10 (4)
A few times a day	38 (14)
A few times a week	16 (6)
A few times a month	24 (9)
A few times a year	23 (8)
Very infrequently	33 (12)
Never	35 (12)
Parts of the phantom limb	
Whole – as it was before amputation	100 (39.1)
Whole – deformed unlike prior to amputation	17 (6.64)
Whole – deformed as it was prior to amputation	2 (0.8)
Distal parts only	107 (47.8)
Proximal parts only	11 (4.3)
Posture of the phantom	
Normal position	203 (79.3)
Abnormal position	30 (11.7)
No perception	23 (8.1)
Size of the phantom limb	
Smaller	4 (1.4)
Normal size	213 (75.3)
Larger	4 (1.4)
No perception	34 (13.3)
Telescoping	55 (21.6)
Exteroceptive sensations	
Itching	129 (50.0)
Pressure	92 (36.7)
Touch	41 (16)
Temperature–heat	43 (16.6)
Temperature–cold	40 (15.6)
Temperature–heat and cold	12 (4.7)
Temperature–warm	14 (17.6)
Electric sensations	120 (43)
Vibration	32 (11.5)
Pins and needles	49 (17.6)
Prosthesis embodiment	
Phantom embodies prosthesis	23
Phantom disappears when wearing prosthesis	34
Phantom does NOT embody prosthesis	5
No change	111
Other	
Increase in PLS/PLP	25
No phantom limb	30
Missingand/or do not wear prosthesis at all or enough	55
Phantom limb movement	
Voluntary phantom limb movement	132 (47.0)
Spontaneous phantom limb movement	107 (37.8)

rates in early reports have been attributed to the confusion of terminology (RLP,PLP and PLS) and poor sample selection presumably taken from patients requesting for a treatment, which tended to be few due to the social stigma attached to the condition [110]. Factors including age, gender, side, level and cause of amputation do not seem to have an influence on the prevalence of PLP [1], [75] although a prospective study on 85 amputees showed that female upper limb amputees are associated with higher risk of PLP [111]. A clear predisposing factor related to PLP seem to be the presence of RLP [110]. Early literature excluded the presence of phantom limbs and PLP in young children and congenital amputees [36], however it has been later found by others that to a small extent, they occur even in this patient group [38]. Older children and adolescents have been found to suffer from PLP as much as adults [112].

Table 2: Prevalence of Phantom Limb Pain. *Prevalence over time. This table is an adapted version of the one appearing at page 81 in [15].*

Period	Prevalence
1910–1919	Unknown
1920–1929	Unknown
1930–1939	Not Infrequent
1940–1949	1%
1950–1959	1%
1960–1969	5%–15%
1970–1979	35%–50%
1980–1989	50%–85%
1990–1999	70%–85%
2000–2009	50%–80%

There is great uncertainty regarding the onset and duration of PLP. Most often it starts immediately after amputation; however, some authors have reported late onset. For example Rajbhandari et al. [113] who described a case of PLP starting forty-four years after amputation. Late onset can happen in presence of a precipitating factor such as injury to the stump, or development of pathology to the nerves [15]. The long-term time course of PLP is also rather unclear. Whereas some studies report decrease over time in PLP intensity and frequency [114]–[116], others report higher likelihood of PLP when longer time since amputation has passed [84]. Our group has worked with patients reporting constant or increased intensity levels of PLP up to 48 years post amputation [13], [117]. In a prospective study on 526 veterans, PLP disappeared over time in 16% of the subjects, decreased significantly in 37%, remained similar in 44%, and increased in 3% [118]. The frequency of PLP is also extremely variable having constant pain on one end of the spectrum to sporadic short-lasting painful shocks [82]. The pain is usually perceived in the distal part of the phantom. For upper limb amputees this means the palm of the hand and fingers, whereas for lower limb amputees it is the toes, foot, or ankle [94], [115], [116].

The introduction of the McGill Pain Questionnaire (MPQ) by Melzack [119] has played an important role in standardizing the language of qualitative descriptors of PLP. **Figure 7** reports the pain descriptors used in the classic version of the MPQ. The most common descriptors applied to PLP are burning, stabbing, throbbing, cramping, numb, smarting, stinging, throbbing, piercing, and tearing [59], [120]. However, Crawford pointed out that before the advent of MPQ it was common to find more vivid and colorful descriptions. For example the wrinkled, raw flesh, red-hot needles, wet, slimy, swollen, glowing, dry, and furry qualities of

phantoms, were largely documented prior to 1975, the year when the MPQ was institutionalized [15], [107]. Accounts of PLP with a more detailed narrative were also more frequent in the past. An example is the one provided by Russell (1949) reporting a sensations of “reopening of the old wound of his foot, followed by a sensation of blood welling up between his toes” [121].

Oftentimes patients report that the pain resembles pre-amputation pain both in quality and location. Katz and Melzack [122] coined the term ”somatosensory pain memories” in 1990 to indicate painful sensation in the phantom which resemble somatosensory events experienced in the limb before amputation. They interviewed 68 amputees and a total of 57% of those who reported having had pain before the amputation claimed that their PLP was indeed similar in quality and location. Nikolajsen *et al.* [116] asked patients to describe their pain before and after amputation and although 44% of patients claimed that their PLP was similar to the pre-amputation pain, the character of PLP was only similar to actual pre-amputation pain in a minority of patients[116]. Some studies found that PLP was significantly more frequent in the first months post amputation but not after two years in patients who suffered from PLP compared with those who did not [115], [116]. Therefore, although pre-amputation pain seems to play a role in the short-term development of PLP, it is not the only mechanism involved and in the long term the correlation between pre-amputation pain and PLP is not evident.

It has been reported that painful experiences in the phantom limb can be modified or triggered by spontaneous events, autonomic reflexes (e.g. micturition), physical (e.g. weather changes), psychological or emotional factors [123]. Giummarra *et al.* [74] explored triggers of phantom phenomena by surveying 264 upper and lower limb amputees with phantom sensations. The results showed for example that upper limb amputees were more likely to experience weather-induced phantom phenomena than lower limb amputees; traumatic amputees were more likely to report emotional triggers. The correlation between stump pain and phantom pains and phantom painless sensations has been evidenced by different authors [85], [124], [125]. Finally, it has been reported of cases of referred phantom pain in which pain in a phantom arm was associated with myocardial ischemia [126].

To summarize, the purpose of the current chapter was to describe the main features of the experience of phantom phenomena, which can be divided in painful and non-painful phantom sensations. What emerges from this account is that the literature is characterized by contradiction and uncertainty. A possible reason for the contrasting accounts is that PLP is not a single syndrome but a class of syndromes with distinct etiologies, that often share a diagnosis based only on the perceived location of pain.

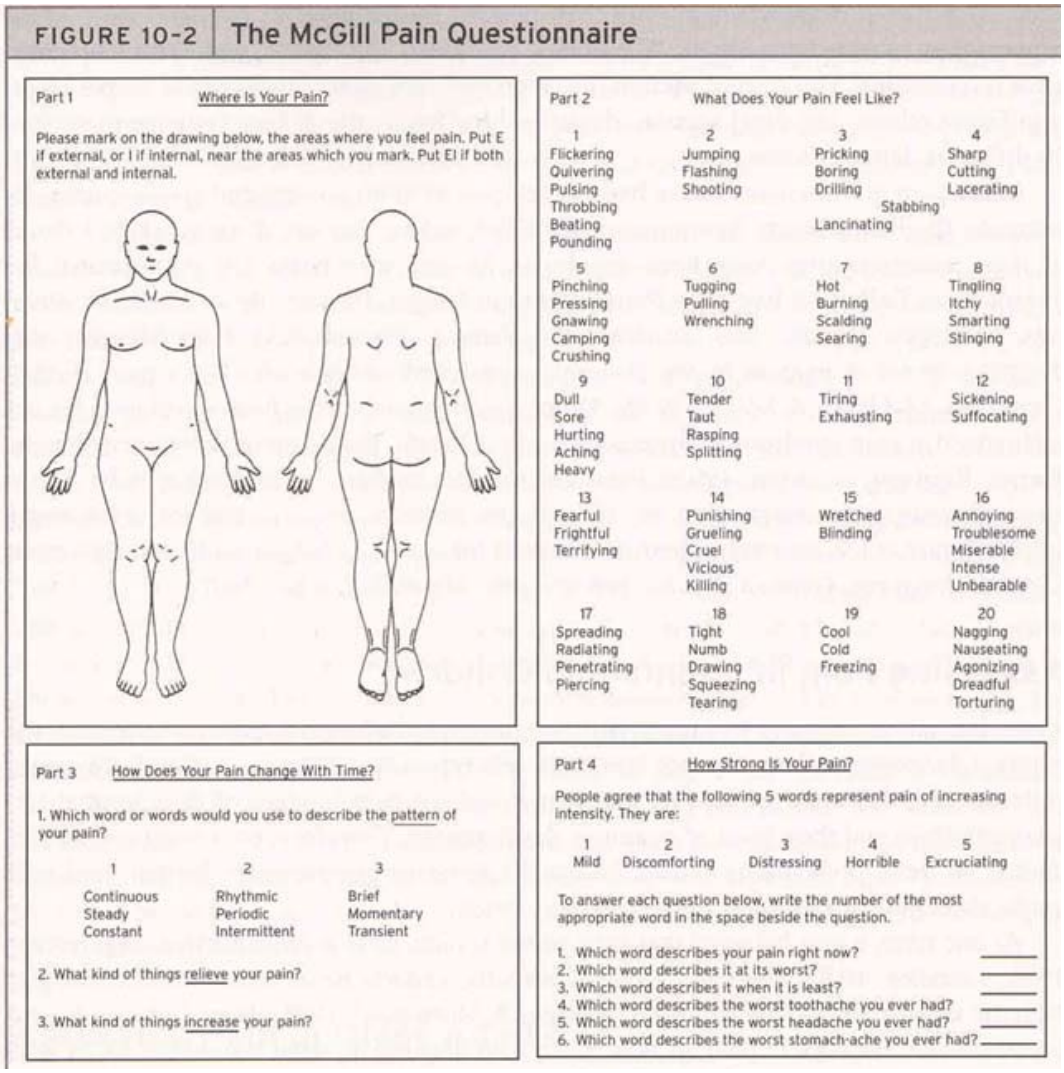

FIGURE 10-2 The McGill Pain Questionnaire

Part 1 Where Is Your Pain?

Please mark on the drawing below, the areas where you feel pain. Put E if external, or I if internal, near the areas which you mark. Put EI if both external and internal.

Part 2 What Does Your Pain Feel Like?

1	2	3	4
Flickering	Jumping	Pricking	Sharp
Quivering	Flashing	Boring	Cutting
Pulsing	Shooting	Drilling	Lacerating
Throbbing		Stabbing	
Beating		Lancinating	
Pounding			
5	6	7	8
Pinching	Tugging	Hot	Tingling
Pressing	Pulling	Burning	Itchy
Gnawing	Wrenching	Scalding	Smarting
Camping		Searing	Stinging
Crushing			
9	10	11	12
Dull	Tender	Tiring	Sickening
Sore	Taut	Exhausting	Suffocating
Hurting	Rasping		
Aching	Splitting		
Heavy			
13	14	15	16
Fearful	Punishing	Wretched	Annoying
Frightful	Grueling	Blinding	Troublesome
Terrifying	Cruel		Miserable
	Vicious		Intense
	Killing		Unbearable
17	18	19	20
Spreading	Tight	Cool	Nagging
Radiating	Numb	Cold	Nauseating
Penetrating	Drawing	Freezing	Agonizing
Piercing	Squeezing		Dreadful
	Tearing		Torturing

Part 3 How Does Your Pain Change With Time?

1. Which word or words would you use to describe the pattern of your pain?

1	2	3
Continuous	Rhythmic	Brief
Steady	Periodic	Momentary
Constant	Intermittent	Transient

2. What kind of things relieve your pain?

3. What kind of things increase your pain?

Part 4 How Strong Is Your Pain?

People agree that the following 5 words represent pain of increasing intensity. They are:

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer each question below, write the number of the most appropriate word in the space beside the question.

1. Which word describes your pain right now? _____
2. Which word describes it at its worst? _____
3. Which word describes it when it is least? _____
4. Which word describes the worst toothache you ever had? _____
5. Which word describes the worst headache you ever had? _____
6. Which word describes the worst stomach-ache you ever had? _____

Figure 7: The McGill Pain Questionnaire*. Reproduction of the McGill Pain questionnaire introduced by Melzack in 1975, reprinted from [119].*

CHAPTER 4

Perception and motor control of phantom limbs

The neurological mechanisms underlying phantom phenomena are not completely understood. In the case of amputation, phantom limbs occur when parts of the peripheral nervous system (PNS) are disconnected from the central nervous system (CNS), causing changes at every level of the nervous system. The purpose of this chapter is to present what is known about perception and motor control of painful and non-painful phantom limbs. However, in order to understand what mechanisms are involved in an abnormal condition such as amputation, this chapter will first provide an overview of basic and well known facts about the normal functioning of the sensorimotor system, which refer to Purves' Neuroscience textbook [127].

Perception

Cutaneous sensation, proprioception and nociception

The somatosensory system provides our brain with information coming from the external world as well as from our own body. This is made possible by the presence of receptors located all over the body, from the surface of our skin to the depth of our internal organs. Somatosensation comprises three different systems: the cutaneous sensory system that senses stimuli applied to the skin; the interoceptive system that provides general information about internal body conditions; and the proprioceptive system that senses the position of body parts. Proprioception and cutaneous senses are particularly relevant to the discussion of what happens when a limb is amputated [127].

The skin mediates a wide range of sensation thanks to the presence of specific receptors that transduce a stimulus into electrical impulses. The type of stimuli that can be transduced are pressure, vibration, skin stretch, heat, cold and chemicals. The receptors transducing these stimuli are usually classified into three categories: mechanoreceptors, transducing mechanical stimuli; thermoreceptors, transducing the temperature information of the stimulus; and chemoreceptors, responding to chemicals. Nociceptors are a subtype chemoreceptors and mechanoreceptors that responds to stimuli potentially damaging to tissue. The experience of pain usually starts with activation of nociceptors. When a receptor is activated by a sufficiently strong (supraliminal) stimulus, it will send the transduced information along the ascending pathway to which it belongs. Nociceptive, temperature, itch

sensations and crude touch follow the spinothalamic tract (in the anterolateral column of the spinal cord) (Figure 8.B [128]) which crosses the midline in the spinal cord and ascend the nervous system in the contralateral side. Conversely fine touch, vibration and proprioception follow the dorsal column–medial lemniscus pathway (Figure 8.A) which crosses the midline more rostrally at the level of the medulla, thus ascending the spinal cord on the ipsilateral side. Because of this special arrangement, spinal hemisection causes a dissociated sensory loss of contralateral pain and temperature sensations, and ipsilateral of fine-touch perception. Both spinothalamic tract and the dorsal column-medial lemniscus pathway consist of a chain of three neurons to convey information from periphery to cerebral cortex. The first order neuron is in the dorsal root ganglia (DRG) and enters the spinal cord via dorsal horns, then following its specific pathway.

First order neurons belonging to the mechanosensory pathway, once in the dorsal horn of the spinal cord continue to ascend the nervous system following the ipsilateral dorsal column up to the brainstem where they then synapse in the caudal medulla with the second order neurons. As already mentioned, here the second order neurons shift to the contralateral side and ascend to the thalamus where they synapse again. From here the pathway continues bringing the information to the primary somatosensory cortex (S1), in the postcentral gyrus.

The S1 is subdivided into four Brodmann's areas (BA), namely 3a, 3b, 1, and 2., which are somatotopically organized—that is, the sensory signals are represented according to where in the body they come from (Figure 9 [129]). BA 3b and BA 1 receive information from receptors in the skin, and BA 3a and BA 2 receive proprioceptive information from muscles and joints, but there are extensive interconnections between these areas.

First order neurons synapse with the second order in already in the dorsal horn of the spinal cord. From that synapsis, the second order fibers cross the midline and ascend the contralateral anterolateral column of spinal cord, projecting to several different structures in the CNS. This broad array of central targets forms an extensive network, also known as pain matrix, that contributes to different aspects of how pain is processed, making pain a multidimensional experience (Figure 10 [130]). In particular, the different central structures that are part of the pain matrix can be group into two main systems: one system mediating the sensory-discriminative aspects of pain perception and the other conveying information about the affective-motivational aspects [131].

The sensory-discriminative system processes location, intensity and quality of the noxious stimulus. Secondary neurons ascending the anterolateral column of the spinal cord project to the thalamus where they make synapse with third order neurons which in turn distribute the signals to S1, respecting the somatotopic arrangement, and secondary (S2) somatosensory cortex [132]. The affective-motivational system is instead responsible for mediating unpleasant feelings and autonomic activations that accompany the exposure to nociceptive stimulation. Second order neurons belonging to this system project to targets in the reticular formation, the superior colliculus, the periaqueductal grey, the hypothalamus and the

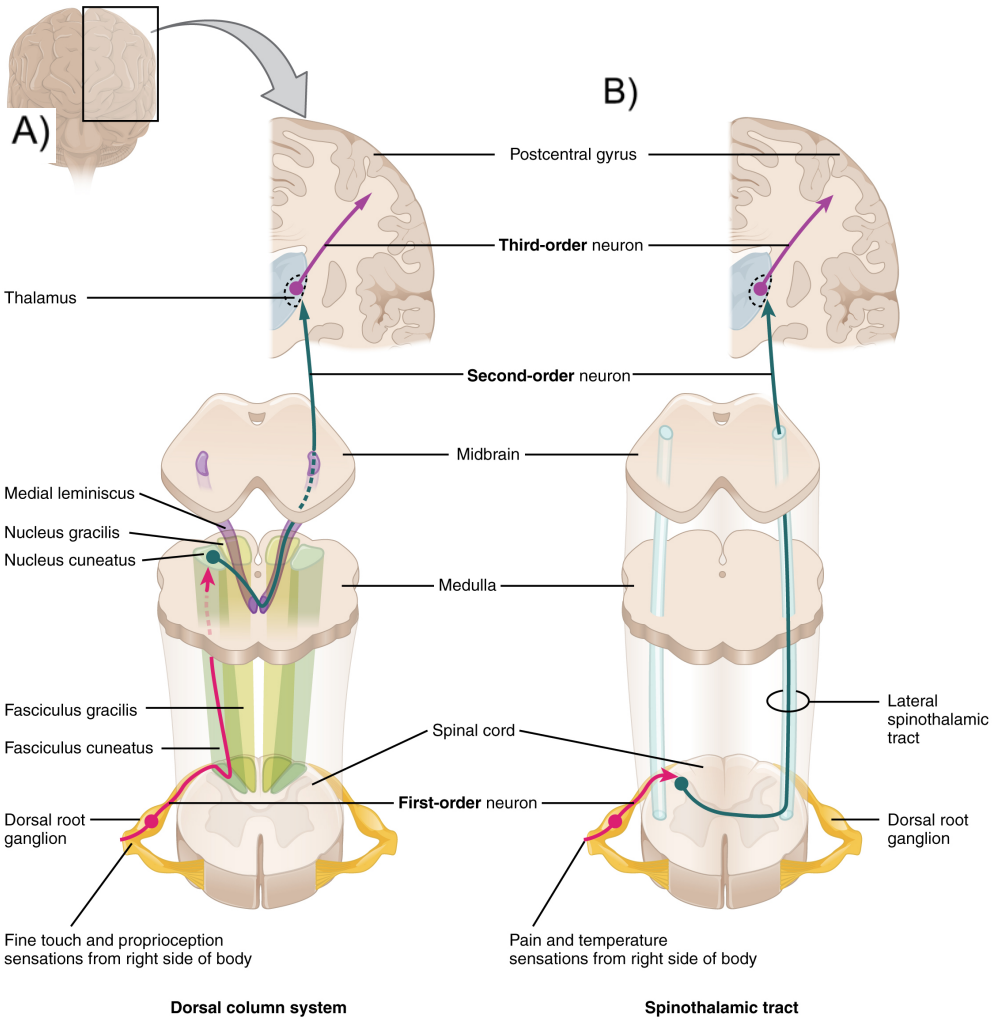

***Figure 8: Ascending sensory pathways**. A) the dorsal column-medial lemniscal pathway, which carries mechanosensory information from the posterior third of the head and the rest of the body. Information from the face is carried by the trigeminal portion of the mechanosensory system. B) The discriminative pain pathway mediating aspects of pain and temperature for the body. Source of the image [128]*

amygdala. Another important target is the thalamus from which third order neurons depart and reach the anterior cingulate cortex (ACC) and the insular cortex (IC) [132].

This view of pain being mediated by two separate systems is consistent with the results of brain imagining studies that have been able to separate the relative contribution to pain perception. By using hypnosis directed to increasing or decreasing the perceived intensity of the burning sensation produced by submerging a subject's hand in painfully hot water, it was found that pain-related activation S1 was modulated [132]. Conversely, hypnosis directed to change the unpleasantness of the perceived sensation had no effect on S1 but produced robust modulation of the activation of ACC, directly correlated to the perception of unpleasantness [133], [134].

Top-down modulation of pain

The perception of pain is also subject top-down modulation, in which higher order brain functions can suppress or amplify sensory information coming from lower order mechanisms. This is possible thanks to descending pathways where several brain areas including the ACC

and IC, the amygdala and the hypothalamus, project to the periaqueductal grey, which in turn regulates the transmission of nociceptive information. For example, it was found that maintaining attention to pain can worsen it [135] whereas distraction can alleviate it [136]. Another factor that is thought to significantly worse pain is pain catastrophizing, defined by Sullivan as “an exaggerated negative mental set, brought to bear during actual or anticipated painful experience”[137]. Distraction was found to be particularly efficacious in relieving pain in these patients. Several studies have also investigated the effect of expectation on pain experience indicating that expecting a pain stimulus exacerbate the actual experience. Similarly, expecting pain relief can ameliorate pain in what is known as placebo effect. The placebo effect is a physiological response following the administration of an intervention, relief is at least partially due to the brain’s own descending modulation circuit [138]. The effects of placebo are real and brain imaging studies have been able to show reduced activity in areas usually involved in pain processing [139] suggesting that this effect is due to the release of endogenous opioids [140].

Finally, another mechanisms for pain modulation initially proposed by Melzack and Wall as gate theory of pain, consists in the modulation of information coming from nociceptive fibres at the level of the spinal cord by the interaction with mechanoreceptive afferences and the circuitry within the dorsal horns [141].

The multitude of areas and targets at all levels of the nervous systems that are involved in pain perception suggests that the full experience of pain is mediated by a cooperative distributed network of brain areas that are often referred to as pain neuromatrix. It should not be surprising then that pain is a multidimensional subjective experience with sensory, emotional, affective and cognitive components.

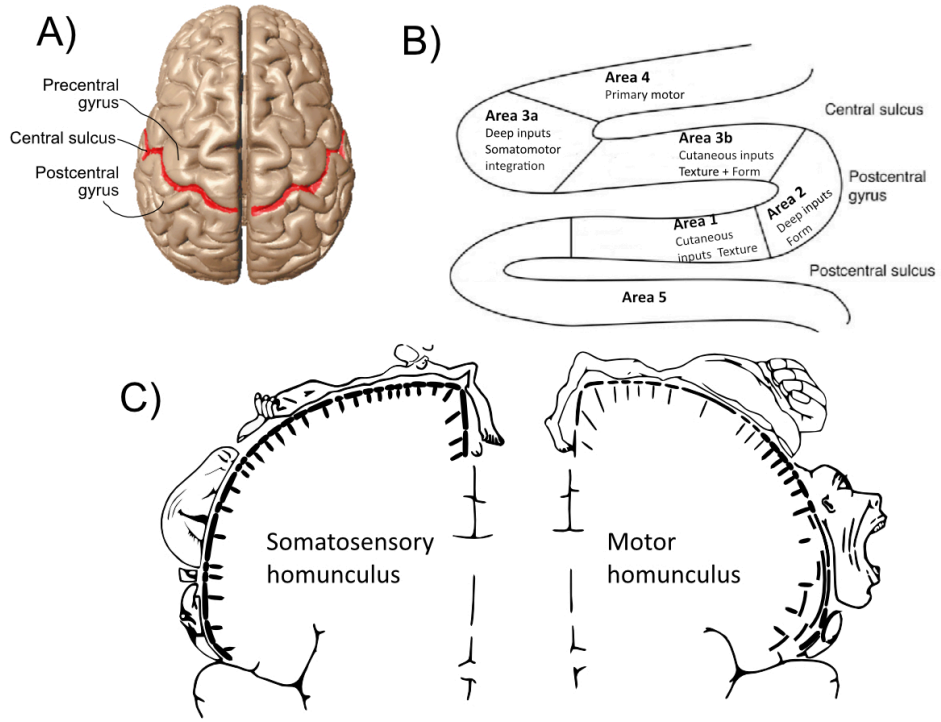

***Figure 9: Sensorimotor maps**. A) Dorsal view of the central sulcus (highlighted in red). B) Sagittal section (along the longitudinal fissure) of precentral and postcentral gyri to highlight the subdivision in Brodman areas. C) Division of sensory (left) and motor (right) functions in the cerebral cortex. Adapted from Penfield and Rasmussen, 1950 [129])*

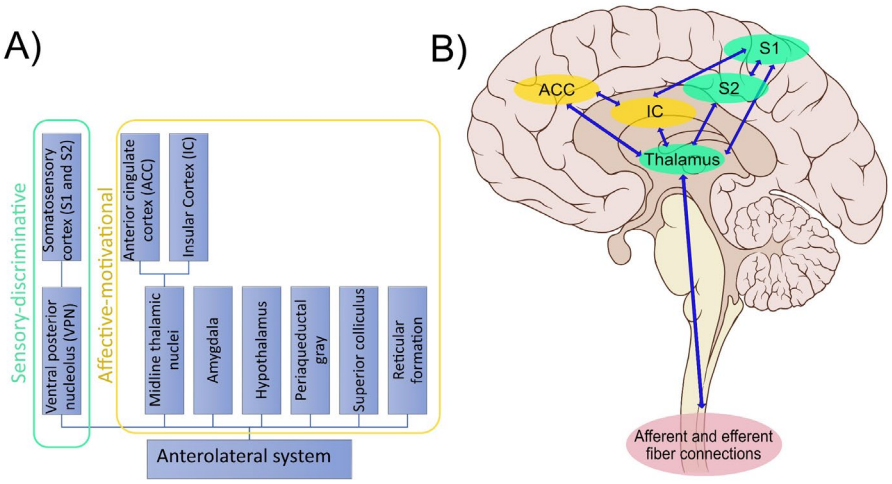

***Figure 10: The experience of pain.** A) A flow diagram showing how the anterolateral system supplies information to different parts of the brainstem and forebrain. B) Detail of the cortical target of the sensory-discriminative (green) and affective motivational (yellow) system. Sagittal view of the brain adapted from [130]*

Neuropathic pain

The International Association for the Study of Pain (IASP) defines nociceptive pain as the pain occurring with a normally functioning somatosensory nervous system in presence of actual or threatened damage to non-neural tissue and is due to the activation of nociceptors. This definition is meant to emphasize by contrast the abnormal function seen in neuropathic pain, which is instead defined as pain arising from lesion or disease of the somatosensory nervous system (Definitions last updated on December 14, 2017).

Nociceptive pain is a physiological sensation aimed at protecting the organism by preventing injury. This is achieved with two strategies: a withdrawal strategy in which a reflex automatically removes the body from the source of the noxious stimulus; and with a protective strategy in which an unpleasant sensation induces the organism to implement complex behavior to avoid further exposure to the source of pain [142]. Another mechanism that further enhances the protective approach is sensitization of the nociceptive system, known as peripheral sensitization, in which repeated, or particularly intense noxious stimuli bring the nociceptors to be more sensitive. A nociceptive stimulus is still necessary to trigger pain; however, the firing threshold of the nociceptors is lower, making them fire following nociceptive stimuli that would normally not be perceived. His condition of heightened sensitivity is also known hyperalgesia. As the injured tissue heals the sensitivity of the nociceptors goes back to normal levels [127].

It can happen however that pain loses its protective function and even non-noxious stimuli. Central sensitization is initiated by activity in nociceptors; however, the effects generalize to other inputs that arise from low threshold mechanoreceptors (allodynia). This feature of central sensitization is caused by means of neural plasticity in the CNS, which changes the sensory response elicited by normal inputs, including those that usually evoke innocuous sensations. Since this effect is cause by plastic changes in the neurons, pain might be experienced long after. Neuropathic pain reflects both peripheral and central sensitization mechanisms [143].

Motor control

Under normal conditions, both voluntary and involuntary movements are the result of patterns of muscle contraction, which in turn are directed by the activity of neural circuits both in the brain and spinal cord. Voluntary movements of the limbs are made possible by skeletal muscles, innervated by lower motor neurons (LMN), that have cell bodies in the ventral horn of the spinal cord grey matter. LMN activation is controlled by local circuits within the spinal cord, which receive direct input from sensory neurons (to mediate the sensory-motor reflexes) and are tightly interconnected. The local circuits of LMN are modulated by upper motor neurons (UMN), whose cell bodies are situated in brainstem centers (such as vestibular nuclei, superior colliculus, reticular formation) as well as in the cerebral cortex which controls the volitional aspect of the movements. Among the cortical areas involved in motor control, the primary motor cortex (M1) and a collection of premotor areas in the frontal lobe, are responsible for planning and controlling complex sequences of voluntary movements. M1, similarly to S1, is arranged according to a somatotopic maps that represent a point to point connection between a certain body part and its respective representation in the cortex. The map seems to represent all the movements that the specific body part can make rather than individual muscles. Also, the larger a cortical area is dedicated to a part of the body the more movements can be performed [144]. The descending pathway that contains the axons of the UMN bringing them to synapse with LMN in the spinal cord is called corticospinal tract (Figure 11 [145]), which is the largest descending tract present in humans [146]. The corticospinal tract is divided into anterior and lateral components. The anterior corticospinal tract innervates both contralateral and ipsilateral axial and proximal limb muscles, securing control of posture and balance. The lateral component of the corticospinal tract innervates the contralateral distal limb muscles thus mediating skilled movements. The decussation of the corticospinal tract takes place at the level of the caudal medulla.

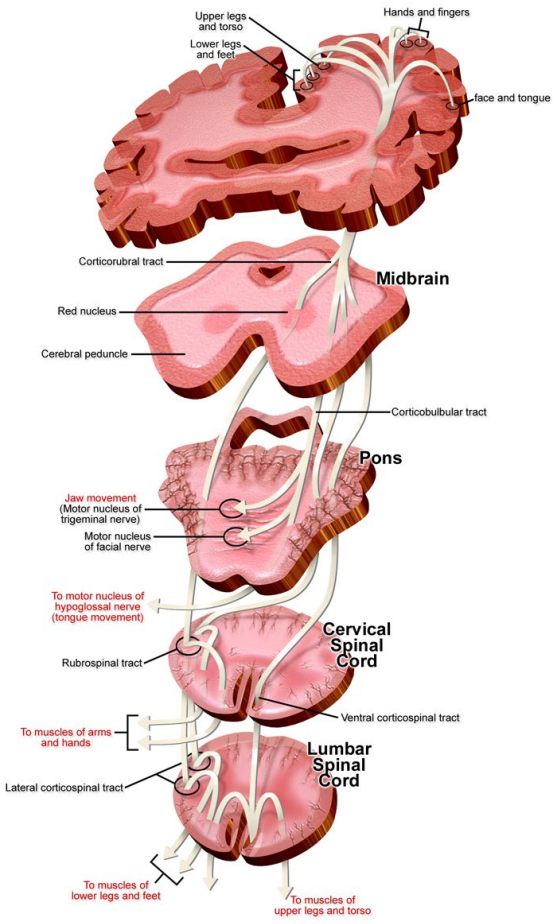

***Figure 11: Descending motor pathways**. Corticospinal and corticobulbar tracts. Source of the picture [145].*

Finally, the neural circuitry in the basal ganglia and cerebellum regulates the upper motor neurons, by projecting to M1 via relays in the ventrolateral thalamus and mediating initiation of movements and regulating the performance [127].

The effects of amputation on the nervous system

Amputation deprives the nervous system of the sensory inputs originating from the detached body part and causes changes at every level of the nervous system. The dynamic ability to change and adapt is called plasticity and can take place both in the periphery [147] and in the central nervous system [127]. This section attempts to clarify the consequences of amputation on the PNS and CNS, and how the mechanisms involved might contribute to the perception of PLS and PLP.

Postamputation pain

Postamputation pain is a composite phenomenon that can have two stages: an acute pain stage sometimes followed by a chronic pain stage. Two types of acute postamputation pain may occur. The first is the pain in the amputated stump, or RLP, and the second is the pain perceived in the missing limb (PLP): these two types of pain are often confused. The acute postoperative pain is due to the damage of the tissue and nerves and it should resolve itself by healing. However, both acute RLP and acute PLP can become chronic. Chronic RLP can have both nociceptive (somatic) and neuropathic origins [148]. Neuropathic mechanisms include the presence of a neuroma, development of Complex Regional Pain Syndrome, heterotrophic ossification or mosaic neuralgia [78]. Nociceptive mechanisms are connected to the failure of the stump to heal and involve infection, failure of flap closure, bone spurs, vascular insufficiency, or soft tissue inflammation around the prosthesis [77]. **Figure 12** shows an adapted version of the proposed classification of postamputation pain phenotypes proposed by Clarke *et al.* [77].

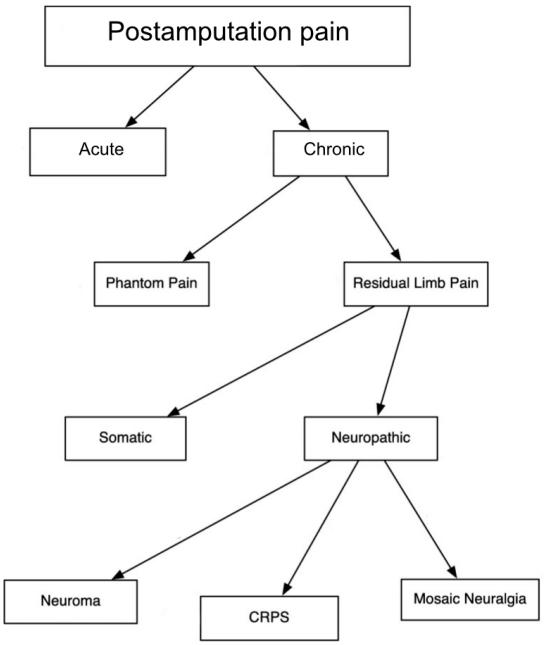

Figure 12:Classification of postamputation pain*. Chart showing the classification of different phenotypes of postamputation.*

Neuroma pain

Among the different phenotypes of RLP, neuroma pain deserves further attention since it can be perceived in the missing limb and thus considered as PLP by definition of the IASP. Diagnosing a neuroma as a source of RLP is however useful when formulation a treatment plan [149]. After disruption of a nerve, axons regenerate and sprout often in an unregulated fashion resulting in a tangle containing axons (both A and C fibres), Schwann cells, endoneurial cells, perineurial cells in a dense collagenous matrix and fibroblasts [120]. Wall and Gutnick [150] showed ongoing spontaneous activity in neuromas, with additional afferent activity, in terms of increased firing rate, generated mechanically (by applying pressure) or chemically (by noradrenaline). Sherman [151] later showed that pain in the phantom can be initiated by spasms in muscles surrounding the neuroma, which would be analogous to applying direct pressure. Further, Nyström and Hagsbarth [152] demonstrated with microelectrode recordings of peripheral nerves in a human amputee, that when using anesthetic block the increased activity evoked by taps on the neuroma was eliminated together with the associated increase of PLP. In contrast, the spontaneous impulse activity in the nerve fascicle was left unaltered by anesthesia together with the spontaneous background PLP. Neuromas can also lead to central sensitization thus causing pain perception in response to stimuli that normally would not provoke pain (e.g. signals coming from fibres other than nociceptive) [153]. The diagnosis of neuroma pain is based on palpation or application of pressure on a focal area of tenderness resulting in a distally radiating pain in the distribution of the peripheral nerve or increase in pain perceived in the stump or phantom.

Stump neuromas have often been hypothesized to be the cause of PLP, and this might indeed be the cause for some patient given the chain of changes in the CNS that a neuroma might trigger (e.g. such as central sensitization). However, neuroma cannot explain the occasional

reports of PLP present immediately after amputation, before a neuroma could possibly form and therefore, neuroma cannot be considered the direct mechanism behind PLP. Another counterexample is provided by some rare case of PLP in congenitally absent limb [154]. Further, despite the fact anesthesia applied to a neuroma can reduce PLP, this does not seem to be the case for all the subjects [152], [155]. Pain perceived in the phantom that is not ascribable to neuroma pain is the type of pain of central interest in this thesis.

Peripheral mechanisms

Early theories attributed the PLS and PLP to the irritation of peripheral nerves. However, these theories have been abandoned over time in light of solid evidence showing that no anesthetic block can universally abolish PLS and/or PLP [155]. Further contributing to the dismissal of PNS as culprit for PLS and PLP, anesthesia was also used in healthy subjects to actually induce phantom limbs [73]. Nevertheless, more recent research as brought the attention to a peripheral mechanism that has so far been unappreciated as a driver of PLP and PLS, namely the ectopic firing of the dorsal root ganglia (DRG). The DRG contain the cell bodies of the first order afferent neurons and belong to the PNS. Following amputation, the DRG lose their receptors of nerve endings and might start firing spontaneously (ectopically), which in turn can amplify the discharges coming from the residual limb or initiate depolarization of neighboring neurons. Vaso *et al.* [156], by performing blockade of the DRG, showed a dramatic relief PLP and a decrease in PLS, thus suggesting that the PNS could be indeed considered as a viable component for a theory of PLP. Finally, events and changes taking place in the PNS may still have a causal role in driving the reorganization of CNS in an experience-dependent manner, thus leading indirectly to the experience of PLP and PLS [120].

Central mechanisms

Kaas and Merzenich (1984) pioneered the analysis of how cortical maps in S1 respond to altered patterned of activity in peripheral nerves in primates. In their work they showed the potential for reorganization of adult cortical circuits, which up to that point were thought to be immutable. To alter the activity of peripheral nerve, they cut the innervation to a hand or amputated a digit. They showed that immediately after the deafferentiation, the cortical area corresponding to the deafferented body part was unresponsive. After few weeks however, they found that area started to respond to stimulation of neighboring body regions. In the case of digit amputation for instance, the representation of the remaining fingers was found to invade the deafferented cortex, in a process also known as functional remapping [157]. Pons *et al.* [41] later discovered more extensive remapping, where the cortical areas related to the deafferented limb became responsive to facial stimulation. Functional remapping has been shown to take place also in the thalamus [158], the brainstem [159] and the spinal cord [160], thus suggesting that some of the cortical reorganization might be indeed induced by the plasticity of subcortical structures [161], [162]. However, it has also been shown that changes at subcortical levels originate in the cortex, thanks to connections to the thalamus and lower structures [163], thus making it difficult to establish a clear direction of causality

Following Pons' observations, Ramachandran (1992) and colleagues hypothesized that phantom limbs could be the perceptual counterpart of this functional remapping and investigated this hypothesis by stimulating the face of two amputees, who consequently

perceived PLS [47]. Several brain imaging studies have demonstrated a shift of the mouth representation into the hand representation in S1 of upper limb amputees [47], [54], [155]. , which has been used to explain phantom phenomena in the context of postamputation reorganization. For example, Flor *et al.* [54] also showed that the perceptual correlated to this reorganization is PLP: the larger the invasion of the mouth into the hand representation, the more intense the pain. This cortical shift, together with PLP, completely disappeared in some patients by using brachial plexus anesthesia that eliminated the peripheral input. This suggests that at least in some cases, cortical reorganization and PLP are maintained by the periphery.[155]. Contributions of subcortical structure to the perception of phantom limbs have been shown by Aydin *et al.* [164] who reported a case of a woman who had suffer from PLP for 60 years and experienced the a progressive decrease in PLP in parallel with the growth of an intraspinal tumor. PLP gradually reappeared after resection of the tumor. Spinal anesthesia has been implicated in the development of PLP, causing it in patients who were previously pain-free [165]. However this doesn't seem to be a reliable effect and the evidence is sparse [166]. Finally, thalamic micro stimulation and recordings in human amputees have shown that the reorganizational changes occurring at the thalamic level are closely related to the perception of PLS and PLP. Thalamic stump representation was found unusually large. Moreover, in amputees with phantom limbs, thalamic stimulation could reliably evoke PLP and PLS even by stimulating those areas responsive to the stump, consistent with the hypothesis that the deafferented neurons remain functionally related to the missing limb.

More recent research conducted with ultra high-field (7T) fMRI confirmed the findings of an earlier pioneering somatosensory evoked potential study that evidenced the continued presence of the limb representation in the deafferented cortex years after amputation [167]. In the recent study, Kikkert *et al.* (2016) showed instead that amputees experiencing highly vivid phantom sensations maintained precise individual finger topography in S1, even decades after amputation and total absence of sensory input [168]. This finding, together with the evidence form structural and functional brain imaging studies corroborate the hypothesis that S1 has limited capacity for reorganization, and that instead, the functional changes previously observed in S1 following deafferentation could be attributed to reorganization in subcortical areas in the afferent pathway, particularly in the brainstem [169].

Motor control of phantom limbs

As already mentioned in Chapter 3, amputees can perceive kinetic sensations of voluntary or involuntary phantom movements [97]. Further, a series of studies investigating both neurological and behavioral aspects of phantom motor control have confirmed that phantom movements are indeed authentic and natural. From a behavioral point of view evidence comes from studies investigating the inter-limb coordination of intact hands and phantoms. Normally, untrained healthy controls when moving both hands simultaneously experience strong coupling effects and neither of the two hands can perform independent actions. This effect has been shown to exist in amputees with phantom limbs when performing the line-circle task, namely drawing a line with either the phantom hand or intact hand and simultaneously drawing a circle with the other side [170]. In the same study it was shown that amputees that could not move their phantom or simply imagined the phantom movement did not show the coupling effect.

Neurological evidence comes from a broad series of studies. For example, intraneural recordings of severed nerves formerly innervating the hand, have shown motoneuron activity associated with missing limb movements. Electrical stimulation of the same nerve was also used to elicit sensations of touch , joint movement and position in the missing limb [171]. Moreover, Electromyography (EMG) activity in stump muscles has also been used as a biomarker of volitional phantom limb movement. In particular, Reilly *et al.* [172] recorded EMG activity from the residual limb muscles of seven upper-limb amputees while they voluntarily produced different phantom limb movements and showed that these phantom movements produced characteristic and repeatable patterns of EMG activity, except for a subject with a frozen phantom who showed always the same EMG pattern regardless of the type of movement attempted. In the same study, Reilly *et al.* [172], induced temporary ischemic block in three amputees in order to eliminate the contribution of stump muscles to phantom limbs movements. This reduced or eliminated the ability to voluntarily move the phantom limb, while reducing also the amplitude of stump muscle EMG activity. This suggests that a motor command must arrive at the selected stump muscles and generate ascending afferent sensory feedback for the amputee to experience movement in the phantom limb.

In another study conducted by the same group [173], M1 area of the deafferented hand was stimulated by using transcranial magnetic stimulation (TMS). This resulted in sensations of movement in the phantom hand accompanied by motor evoked potentials in stump muscles. Further, phantom limb movements that were not accessible by the amputee under normal conditions, could be executed under TMS, thus suggesting that the inability to voluntarily move the phantom limb is not due to a loss of the corresponding movement representation but its impairment. Taken together, these findings seem to suggest that the representation of phantom movements is preserved within M1 and are expressed by retargeting residual limb muscles [174]. The mechanisms allowing for this retargeting and the level at which this happens (i.e. centrally or in periphery) are yet to be elucidated. However Reilly at al.,[174] hypothesized that M1 representations of the deafferented limb survives automatically after amputation, and under certain circumstances, spinal, subcortical, and/or cortical reorganization allow these preserved representations to express themselves within a new sensorimotor loop by contacting stump muscles, which by activating produce a sensory afference in return. They further suggest that such mechanism could provide advantage to the amputee in the form of PLP relief. In a follow-up brain imaging study conducted by the same group, Raffin *et al.* [11] conducted a study that provided evidence for a link between phantom motor control and PLP. They showed that the amputated limb representation was preserved in M1 and symmetrical to the representation of the healthy side. Further they showed that poorer voluntary control and higher levels of pain in the phantom limb were linked lip and elbow representations reorganization, which were found to be shifted towards the amputated hand area. Other studies have corroborated the evidence that worse chronic PLP is associated to poorer and/or slower phantom motor control [12], [175], [176].

Additional support for the hypothesis that M1 representation of the hand is preserved following deafferentation comes from other brain imaging studies showing that movement-related activity of the phantom hand in amputees is compatible to that of two-hander controls when moving their non-dominant hands [55], [168]. However, in contrast to the findings of

Raffin *et al.*[11] with respect to PLP, Makin *et al.*[55] show that PLP is correlated instead to persistent representation of the phantom motor representation which is maintained by the experience-dependent plasticity induced by pain itself. They further found that PLP is associated with reduced interhemispheric functional connectivity between the phantom cortex and intact hand cortex, hypothesizing the experience of pain as a contributor to the functional decoupling from the sensorimotor network.

In this chapter, the main aspects involved in the perception of phantom limbs and PLP, together with an overview of what is currently known regarding the neural basis of phantom motor control were summarized. At the current state, it seems that both peripheral and central mechanisms are involved these phantom phenomena. Recent findings showing dramatic relief from both PLP and PLS following blockade of the DRG [156] suggest that role of peripheral factors in PLP might have been so far underestimated, however to conclusively show the PLP depends solely on ectopic discharges from the PNS further evidence is required. Central aspects of phantom phenomena are more contradictory and involve reorganization of S1 and S2 (maladaptive or experience-dependent) and possible reorganization at every subcortical level.

CHAPTER 5

Theories of pain and hypothesis of PLP

The present chapter provides an overview of the current theoretical frameworks and the most plausible hypothesis accounting for the origin and maintenance of PLP.

Neuroplasticity

Maladaptive plasticity and cortical reorganization theory

The cortical reorganization theory emerged following Flor *et al.* (1995) seminal work, where a strong correlation between the intensity of PLP and the amount of cortical reorganization was found [54]. The reorganizational changes that they observe related to the invasion of the S1 deafferented cortex from neighboring cortical representations. Other studies replicated the finding in S1 [177], [178] and further showed similar reorganizational patterns into M1 cortex [179]. Later it was observed that reduction of PLP was accompanied by a rather quick normalization of the cortical representation [155]. Further reduced reorganization and PLP was also shown after functionally relevant sensory discrimination training [180] and intensive use of a myoelectric prosthesis [181]. Nonetheless a recent systematic review of fMRI studies assessed the robustness of the evidence in favor of the maladaptive plasticity model and found only limited evidence in support of the theory and highlighting the need for further studies, in particular longitudinal studies assessing pain-modulating intervention [182].

Importantly, the cortical reorganization theory does not imply that invasion of the deafferented cortex leads to a loss of phantom representation. This has been demonstrated by brain imaging data showing maintained SM1 phantom limb representation within the original cortex together with the typical link between PLP and cortical reorganization postulated by the theory [183]. This view is also consistent with the suggestion advanced by Merzenich *et al.* [40] that reorganization following sensory input loss does not dismiss the possibility for coexistence of the original function.

The findings of Flor *et al.* [54] themselves cannot establish a causal link between reorganization and PLP. However, the authors proposed that loss of sensory inputs to the phantom cortex, an adaptive process meant to recover functionality takes place. In amputees with PLP this process may have become maladaptive and associated to pain maintenance. The maladaptive changes may also have origins in lower level structures. What remains unclear in

the maladaptive cortical reorganization model is the explanation of precise mechanism (direct causality of mediation by a third party) at the basis of the strong correlation between PLP and cortical reorganization.

Experience-dependent plasticity driven by pain

This theory, known as the persistent representation model, was first proposed in Makin *et al.* (2013), as interpretation of their fMRI study comparing PLP patients with congenital one-handers without PLP and healthy controls. The study found that stronger activations in SM1 following phantom execution were correlated with the amount of PLP experienced by amputees. They also showed that the amount of grey matter volume was reduced in paitents with pain, and this structural change was also correlated to PLP. Finally, the same study also showed a reduction of interhemispheric connectivity between the SM1 phantom and intact hand representation in presence of PLP. A behavioral counterpart of this effect could potentially be the reduced bimanual coupling of patient with PLP presented by Osumi *et al.*[184]. The theory attributes all the effects found in that study to experience-depended plasticity driven by PLP, which in turn could be triggered either bottom-up peripheral inputs (e.g. ectopia in the DRG [156]) or top-down inputs coming from other pain-related brain areas (e.g. insula). By being the experience that drives plasticity, PLP maintains the local cortical representation and disrupts the functional connectivity between the missing hand cortex and the sensorimotor network [185]. Coherently with this hypothesis, studies conducted by the same group showed that higher PLP correlates with worse motor control of the phantom limb, which in turn produces stronger SM1 activation [12] and induced PLP relief is conversely associated with decreased activity [186].

Neuromatrix

In 1990 Melzack proposed the neuromatrix theory to account for the perception of phantom limbs and associated pain [95]. However, the theory become later on used to account for body perception, somatic sensations and pain perception [187]. What brought Melzack to propose the neuromatrix theory was the impossibility of identifying phantom phenomena with S1, due to the failure of procedures such as S1 ablation for PLP treatment to eliminate both phantom limbs and PLP. Instead of considering single stimuli to different areas of the brain as the ingredients of conscious perception, he proposed that the experience of the body emerges from a genetically built-in matrix of neurons for the whole body that he renamed “the self-body neuromatrix” (**Figure 13**). Practically, this neuromatrix has been hypothesized to be a network of neurons in several brain areas including the thalamus and somatosensory cortex, the reticular formation, the limbic system, and the posterior parietal cortex, that are the anatomical substrate of the self. Said neuromatrix takes several different inputs and it outputs characteristics nerve-impulse patterns that account for everything we feel (neurosignatures). The landmark feature of the neuromatrix theory is that a single input can only trigger or modulate a neurosignature and cannot directly cause perception. The implications of this theory for pain are that a noxious stimulus might not be necessarily felt (it might not trigger a pain neurosignaure) and in the same way the pain neurosignature might be active without a stimulus that triggered it. Similarly, an amputation causes changes in the sensory inputs that

lead to an altered neurosignature which in turn could result in phantom phenomena (painful and non).

A limitation of the neuromatrix theory is that although it offers a complex account of pain, potentially explaining every aspects, this theory is highly unspecific and hard to test empirically because it does not give an account of how everything actually happens (e.g. how neurosignatures are formed and activated). Consequently, it does not give any clear direction on how to treat PLP: it just emphasizes the need to treat PLP with a holistic approach that encompasses the equally important cognitive, affective and sensory factors.

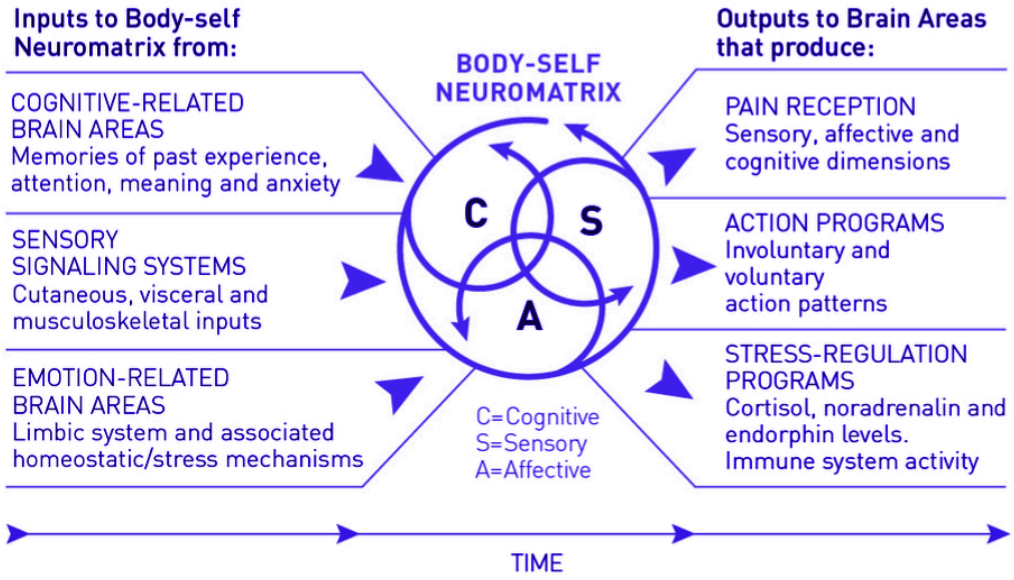

Figure 13: Pain neuromatrix. *Factors that contribute to the patterns of activity generated by the body-self neuromatrix, which comprises sensory, affective, and cognitive neuromodules. The output patterns from the neuromatrix produce the multiple dimensions of pain experience as well as concurrent homeostatic and behavioral responses. Source [187].*

Stochastic entanglement

Recently a new hypothesis was proposed by Ortiz-Catalan [10]. This hypothesis, named *stochastic entanglement*, could be regarded as an evolution of the neuromatrix theory of pain with regards to the existence of pain neurosignatures, but accounting for the dynamics leading to their unintended activation. According to the hypothesis, the nervous system can be assimilated to a complex dynamical system, that if seriously perturbated (i.e. by amputation) enters a susceptible state (disequilibrium) where different brain networks (e.g. sensorimotor network and pain network) can become unintentionally entangled due spurious firing coinciding temporally and spatially. For example, if the pain neurosignature is entangled with the sensorimotor network, PLP could be experienced. Similarly to Melzack's neuromatrix theory, the stochastic entanglement can fully account for the multidimensionality of the experience of pain, including emotional and cognitive components. A fundamental feature of

this hypothesis is that the long-term evolution of the system depends on its initial conditions, thus accounting also for the portion of patients who never develop PLP (which is something currently unaccounted for by other hypothesis and theories of PLP). Another important feature of the stochastic entanglement is the clear prediction that PLP should be relieved by undoing the entanglement, in a process akin to the inverse of Hebb's law "neurons that fire apart wire apart". Ways of disentangling pain and sensorimotor circuitry could be by reengaging the sensorimotor network in a functionally meaningful way. Phantom Motor Execution (PME), the exercise of voluntary and skilled phantom movements, is the proposed way to achieve this.

CHAPTER 6

Summary of Included Papers

This chapter provides a brief summary of the papers that constitute the basis for this thesis. Full versions of the papers are included in Part II.

Paper A

E Lendaro, E Mastinu, B Håkansson, M Ortiz-Catalan

Real-time classification of non-weight bearing lower-limb movements using EMG to facilitate phantom motor execution: engineering and case study application on phantom limb pain *Published in Frontiers in Neurology, 2017, 8:470*.

DOI: https://doi.org/10.3389/fneur.2017.00470

The evidence in support of PME as an effective way to treat PLP was initially obtained only on upper limb amputees. However, lower limb amputees represent the vast majority of cases of limb loss. In order to investigate the effectiveness of PME in lower amputees, the system in use for treating upper limb patients needed to be adapted. The first aim of this study was to enable PME aided by MPR and VR/AR in lower limb amputation. This resulted in the proposal and validation of a new recording configuration that is a more user-friendly to record EMG signals from the lower limb. Further, the second aim of the paper was to provide evidence that PME is a viable option for PLP relief in lower limb amputees, and therefore the successful treatment of the first lower limb patient conducted. Enabling and verifying the treatment for lower limb patient was an instrumental step for the RCT on the use of PME, the protocol of which is presented in paper B.

Paper B

E Lendaro, L Hermanson., H Burger , C Van der Sluis C., B McGuire, M Pilch, L Bunketorp-Käll, K Kulbacka-Ortiz, I Rignér, A Stockselius, L Gudmundson, C Widehammar, W Hill, S Geers, and M Ortiz- Catalan

Phantom Motor Execution as a treatment for Phantom Limb Pain: Protocol of an international, double-blind, randomized, controlled clinical trial *Published in British Medical Journal Open, 2018, 8:e021039*

DOI: http://dx.doi.org/10.1136/bmjopen-2017-021039

Despite the large number of treatments described in the literature to treat PLP, none of them has proven to be decisively effective for treating the condition, and at present, guidelines for the treatment of patients in this situation are absent. This can be largely attributed to the scarcity of RCTs on such treatments. In this paper, we designed the protocol for a double blind, international, multi-sited RCT on the use of PLP in order to gather unbiased and stronger evidence of the actual effect of PME. This is to the best of our knowledge, the largest international clinical trial on PLP ever conducted.

Paper C

E Lendaro, A Middleton., S Brown, M Ortiz-Catalan

Out of the Clinic, Into the Home: The In-Home Use of Phantom Motor Execution aided by Machine Learning and Augmented Reality for the treatment Phantom Limb Pain *Published in Journal of Pain Research, 2020, 13, 195*.

DOI: https://doi.org/10.2147/JPR.S220160

Preliminary evidence suggests that in order to maintain long term PLP relief, periodic rehearsal of the phantom motor skill is necessary. In this study we enabled the treatment to be self-administered and carried out at home and we investigated how patients adapted to the regime. The purpose here was to explore the benefits and the challenges encountered in translation from clinic to home use with a mixed-methods approach, employing both quantitative and qualitative methods from engineering, medical anthropology, and user interface design.

CHAPTER 7

Concluding Remarks and Future Works

Looking back at the work done so far and presented in this licentiate thesis, a theme emerges: this time has served to "set the stage" for the final PhD defense. In paper A, we have extended the use of PME to lower limb patients, this step was necessary in order to carry out the RCT. Paper B has presented the preparatory work for this clinical trial which is currently carried out and in completion phase: most of the planned patients have already been treated and the last follow-up assessment are expected to carried out in March 2021. Finally, paper C enabled PME to be used by the patients themselves, at their homes, investigating the benefits and challenges of a transition from the clinic to home, and served to identify what could be improved in order to ensure treatment adherence.

The future work involves the completion and presentation of the results of the RCT. However, as I briefly mentioned in Chapter 1 when providing the motivation for this thesis, having a way to modulate PLP represents a unique tool for studying the neural basis of PLP. Capitalizing on this tool, we are currently running brain imaging studies based on fMRI and electroencephalography, which will be the main focus of the work lying ahead.

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Part II

Included Papers

PAPER A

Real-time classification of non-weight bearing lower-limb movements using EMG to facilitate phantom motor execution: engineering and case study application on phantom limb pain

E Lendaro, E Mastinu, B Håkansson, M Ortiz-Catalan

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Real-time Classification of Non-Weight Bearing Lower-Limb Movements Using EMG to Facilitate Phantom Motor Execution: Engineering and Case Study Application on Phantom Limb Pain

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Phantom motor execution (PME), facilitated by myoelectric pattern recognition (MPR) and virtual reality (VR), is positioned to be a viable option to treat phantom limb pain (PLP). A recent clinical trial using PME on upper-limb amputees with chronic intractable PLP yielded promising results. However, further work in the area of signal acquisition is needed if such technology is to be used on subjects with lower-limb amputation. We propose two alternative electrode configurations to conventional, bipolar, targeted recordings for acquiring surface electromyography. We evaluated their performance in a real-time MPR task for non-weight-bearing, lower-limb movements. We found that monopolar recordings using a circumferential electrode of conductive fabric, performed similarly to classical bipolar recordings, but were easier to use in a clinical setting. In addition, we present the first case study of a lower-limb amputee with chronic, intractable PLP treated with PME. The patient's Pain Rating Index dropped by 22 points (from 32 to 10, 68%) after 23 PME sessions. These results represent a methodological advancement and a positive proof-of-concept of PME in lower limbs. Further work remains to be conducted for a high-evidence level clinical validation of PME as a treatment of PLP in lower-limb amputees.

Keywords: phantom limb pain, virtual reality, myoelectric control, electromyography, pattern recognition, neurorehabilitation, phantom motor execution

INTRODUCTION

Following an amputation, it is common for the patient to perceive the missing limb as if it is still part of the body. The phenomenon, known as phantom limb, is accompanied by a wide range of sensory perceptions that can vary among patients but are collectively referred to as phantom sensations (such as warmth, cold, or kinesthesia) (1). Amputees can often experience painful sensations in their phantom limb, giving rise to a condition commonly known as phantom limb pain (PLP). The pathogenesis of PLP is still controversial, and there is currently no treatment regarded as generally effective. Therefore, PLP remains a major clinical challenge (2, 3).

Recently, promising results on the treatment of PLP were achieved with a novel technology tested on subjects with upper-limb amputation (4). This treatment, firstly introduced by Ortiz-Catalan et al. in 2014 (5, 6), aims at promoting the execution of phantom movements, and hence the name phantom motor execution (PME). Other contemporary research efforts have brought about a number of non-pharmaceutical initiatives to treat PLP focusing on voluntary or imagined phantom movements (7–11). PME distances itself form these approaches by the certainty it provides of phantom movements being actually executed, while visualized as direct biofeedback with unperceivable delay. This is achieved using a myoelectric pattern recognition (MPR) system that renders virtual and augmented reality (VR/AR) environments under the control of the subject's phantom limb. For instance, a virtual arm superimposed on a live video projection of the patient's stump can be controlled in a similar way as the patient's arm prior to amputation. The advantage of such a system is twofold. First, the ease of movement of the virtual limb is a direct consequence of naturalistic muscular patterns of activation owing to the nature of MPR. Second, VR and AR environments provide visual feedback that is congruent with the phantom motion executed, thus facilitating motor execution (12, 13). Clinically significant improvements on PLP (approximately 50% reduction) found in upper-limb amputees treated with PME (4) call for this technology to be explored in lower-limb amputees suffering the same condition.

For many decades, MPR has been vastly studied for upper limbs (14), while advances for lower limbs are relatively recent and mostly focused on improving prosthetic control under weight-bearing conditions (15–20). However, in the context of implementing *PME* for lower limbs, the interest in MPR lies in non-weight-bearing conditions because the patient should be able to execute leg movements while sitting in front of a screen. More importantly, such movements must be natural, not the result of reaction forces. MPR for the non-weight-bearing condition has been attempted in offline (21) and real-time studies (22). Notably, Hargrove et al. demonstrated the discrimination of eight leg movements (knee flexion/extension, ankle plantarflexion/dorsiflexion, hip rotation medial/lateral, and tibial rotation medial/lateral) in both non-amputee and amputee subjects by recording surface electromyography (sEMG) signals with bipolar electrodes placed over nine residual thigh muscles (22). The adopted procedure for electrode placement and signal collection can be challenging in a rehabilitative setting. Primarily, not all muscles might be available depending on the level of amputation. Furthermore, anatomical changes following amputation could make it difficult to precisely identify the desired muscles.

We previously proposed two electrode configurations to acquire sEMG for MPR of non-weight-bearing movements of the lower limb (**Figures 1A,C**) (23). We compared these electrode configurations with the conventional bipolar targeted configuration in terms of signal-to-noise ratio (SNR) and offline MPR classification accuracy. We found that equally spacing the electrodes round the most proximal third of the thigh is a viable alternative to bipolar recordings from specific muscles, with the additional advantage of facilitating the recording procedure. However, MPR offline accuracy does not necessarily correspond with real-time performance (24–26). In this work, we validated previous offline findings using real-time metrics and performed the first clinical evaluation of *PME* on a lower-limb amputee who suffered from chronic, intractable PLP.

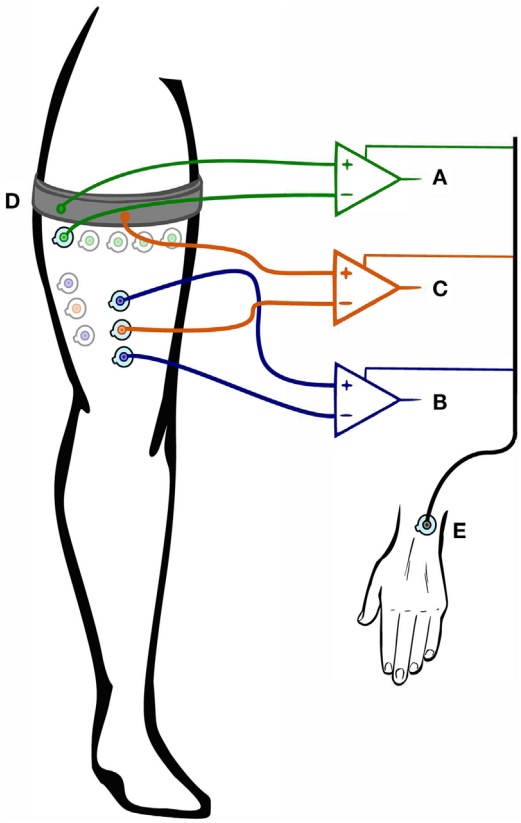

FIGURE 1 | Sketch of the three electrode configurations. **(A)** Untargeted monopolar configuration, **(B)** targeted bipolar configuration, **(C)** targeted monopolar configuration, **(D)** common circumferential electrode, and **(E)** reference electrode.

Ethical approval for the studies was granted by the ethical committee of Västra Götalandsregionen. The participants in both studies signed informed consent statements. The patient who underwent *PME* treatment was also informed of possible increases in pain, and uncertainty of positive outcomes.

MATERIALS AND METHODS

Part I: Classification of Non-Weight-Bearing Lower-Limb Movements

The Subjects

Twelve non-amputees (five males and seven females, ages 23–30) and two amputees participated in the study. One amputee had a unilateral transfemoral amputation (70 years old and 35 years after amputation), whereas the other had a unilateral, transtibial amputation (72 years old and 22 years after amputation). The transfemoral amputee was trained in using the MPR system, while the transtibial amputee was a novice.

Electrode Placement

Non-amputees sat on a raised seat, allowing their feet to hang freely. This precaution was taken to ensure that patterns used for discriminating movements of the foot (ankle plantarflexion/dorsiflexion) were not generated by ground reaction forces. In one experimental session, sEMG signals using a targeted bipolar configuration (TBC) and a targeted monopolar configuration (TMC) were simultaneously acquired. In a different session, an untargeted monopolar configuration (UMC) was used (**Figure 1**). Amputees participated in both experimental sessions on two different days, and non-amputees were randomly divided into the two sessions (six each). **Figure 1** shows the recording configurations as follows:

- *UMC* (**Figure 1A**): a circumferential electrode made of conductive fabric (silver-plated knitted fabric) was dampened with a small amount of water to decrease skin-electrode impedance and tied around the most proximal third of the thigh. Sixteen Ag/AgCl adhesive electrodes (disposable, pre-gelled Ag/AgCl, 1-cm diameter) were placed below the band (more distally on the leg) and equally spaced around the thigh. The gap between the electrodes and the band was approximately 4 cm. Differential measurements were recorded between each of the electrodes and the common circumferential electrode (CCE) (**Figure 1D**). The configuration is monopolar, due to the use of the CCE as a reference for the other adhesive electrodes.
- *TBC* (**Figure 1B**): eight pairs of pre-gelled electrodes were placed over the following eight muscles at an inter-electrode distance of 4 cm: sartorius, tensor fasciae latae, vastus medialis, rectus femoris, vastus lateralis, gracilis, the long head of the biceps femoris, and semitendinosus. The stump of the transfemoral subject was long enough to identify all the muscles.
- *TMC* (**Figure 1C**): for each pair of electrodes in the TBC, a third electrode was placed in between. The CCE was dampened and tied around the proximal third of the thigh. We recorded differentially between each of the eight electrodes and the average potential of the area covered by the CCE.

A reference electrode used for all recording configurations was placed on the contralateral wrist over the distal end of the ulna (**Figure 1E**).

Recording Session

The system used for sEMG acquisition was developed in-house and based on the RHA2216 chip (Intan Technologies, USA), with embedded filter (a third-order, Butterworth, low-pass filter with cutoff at 750 Hz and a first-order, high-pass filter with cutoff at 1 Hz). The system amplified the myoelectric signals from 16 channels with a gain of 200 times, and digitalized them with 16 bits of resolution at a 2-kHz sampling rate. Before proceeding to data acquisition, sEMG signals from all channels were checked to ensure the devise was functioning correctly. The data acquisition, signal treatment, pattern recognition, and real-time evaluation all used an open-source software (BioPatRec) for decoding motor volition using MPR (25).

The participants were instructed to follow a graphical user interface showing the movements to be performed (**Figure 2**), along with a progress bar signaling the duration of each contraction. The recorded movements were as follows: knee flexion/extension, ankle plantarflexion/dorsiflexion, hip rotation medial/lateral, and tibial rotation medial/lateral. The amputees were asked to execute the movements as naturally as possible, focusing on their phantom leg. All participants were also instructed to perform the movements at a comfortable speed, avoiding abrupt contractions or jerks, as these would introduce motion artifacts in the signals. Once participants reached the end of their range of motion, they held the position for the remaining part of the contraction time, and then relaxed. For each movement, sEMG signals were collected in three consecutive repetitions of 4 s each, in which each repetition was followed by 4 s of rest. The subjects were asked to execute the movements at approximately 70% of their maximal voluntary contraction (according to their subjective estimation) to prevent premature fatigue. Before proceeding with the actual data collection, each subject executed one preparatory recording session to become familiar with the system. The recordings are available online in the repository of bioelectric signals of BioPatRec, under the name *8mov16chLowerLimb* (27).

Signal Treatment

Data recorded during the contraction time usually contain absent or transient sEMG signals due to a delay between the movement prompt and the actual execution, or anticipatory relaxation of the muscles. We reduced the impact of ambiguous information by discarding 15% of the signal at the beginning and at the end of the contraction time. This yielded trimmed contraction periods of 2.8 s each, which were then concatenated resulting in 8.4 s of total contraction signal. The signal obtained was subsequently divided, or segmented, into time windows of 200 ms, with 50 ms time increment. The segmentation produced 163 time windows for each movement, and from each time window four sEMG signal features were extracted per channel (mean absolute value, wave length, slope changes, and zero crossings) (28). The features extracted from all channels in a given time window formed a feature vector. The 163 features vectors corresponding to each time window were then randomly assigned to the classifiers' training, validation, and testing sets in the following respective proportions: 40, 20, and 40% (25).

Classifier Training and Real-time Evaluation

The "rest" condition was considered as a movement or class, resulting in a classification task of nine patterns. Linear Discriminant Analysis in a One-Vs-One topology (LDA-OVO) was used for classification (5, 6). Immediately after the classifier was trained, the real-time performance in each electrode configuration was evaluated with the Motion Test (29), as it is implemented in BioPatRec (25). The Motion Test asks subjects to execute the trained movements that are presented to the user in random order Subjects performed the test twice. The following metrics were then evaluated:

- *Selection time*: time elapsed between the first prediction different from rest and the first correct prediction. The shortest selection time possible was 211 ms (200 ms of the first time window plus the processing time before the prediction is available).

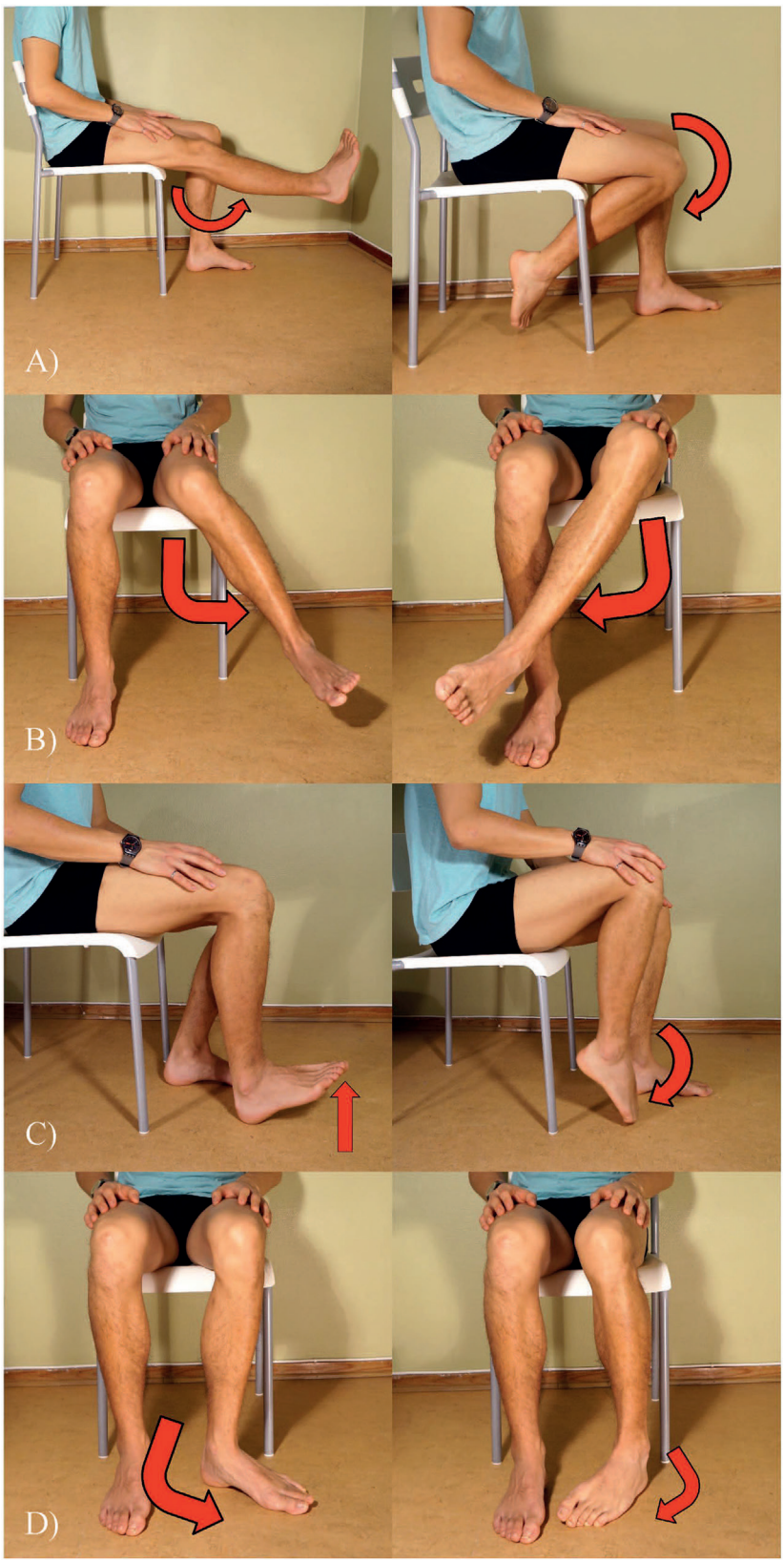

FIGURE 2 | Photographs depicting the trained motions **(A)** knee extension and flexion, **(B)** femoral rotation outwards and inwards, **(C)** ankle plantar flexion and dorsiflexion, and **(D)** and tibial rotation outwards and inwards.

- *Completion time*: time elapsed between the first prediction different from rest (as in the selection time) and the 20th correct prediction. The shortest completion time possible was 1.16 s.
- *Completion percentage*: the percentage of motions that were completed; or the motions that reached 20 correct predictions before the 10 s timeout.
- *Real-time accuracy*: only calculated for completed motions and accounts for the number of predictions needed to obtain 20 correct predictions. For example, if the completion time took 25 time windows, the real-time accuracy would be 80%.

The order in which Motion Tests were performed was randomized within the TBC and TMC groups. Two conditions were evaluated in random order with the UMC session: all 16 channels; and a subset of equally spaced 8 channels.

Statistical Analysis

We investigated the real-time performance of two alternative electrode configurations (TMC and UMC) to the conventional, TBC. Testing for statistical significance was conducted only on the non-amputees owing to the small sample size of the amputee group, in which case-only descriptive statistics were used. The TBC and TMC configurations were investigated on the same subjects, and the classifier for the real-time classification task was trained using data collected within the same recording session. Consequently, the two groups were compared by using the Wilcoxon signed-rank test. The UMC configuration was analyzed on a different set of subjects. The comparison between TBC and UMC with 8 channels (UMC-8 ch), and the one between UMC-8 ch and TMC were performed with Wilcoxon rank sum test for independent samples. In addition, UMC was investigated in two variants, with 8 and 16 channels, to determine if additional channels could improve performance, as tested with Wilcoxon signed-rank. Statistical significance was considered at $p < 0.05$ with Bonferroni correction.

Part II: Case Study on a PLP Sufferer

The Subject

A 70-year-old male with traumatic transfemoral amputation (unilateral) took part in the pain treatment case study. The subject described his phantom leg as of the same length as his normal leg and located the phantom pain in the foot (**Figure 3**, location 5). The PLP had been present since the amputation 35 years ago. However, the overall pain intensity had increased over the years, despite the implantation of a spinal cord neurostimulator 10 years prior to the start of our investigation. The participant described the pain as sustained low intensity pain, mainly present during the day, and recurrent high intensity pain, predominant in the evenings and at night. During periods of strong pain, the subject would feel the need to stand up, walk around, and use the neurostimulator. As a result, his sleep was disturbed by pain seizures that would wake him up and make him unable to sleep for more than 2 h per night.

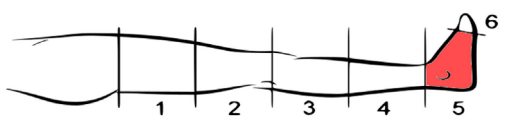

FIGURE 3 | Representation of the phantom limb pain location in the lower-limb amputee subject treated with *phantom motor execution*.

The *PME* Treatment

The patient received *PME* interventions twice per week, for a total of 23 sessions. Each session lasted approximately 2 h, starting with pain assessment and continuing with *PME*. PLP was also monitored at 1, 3, and 6 months after the last treatment session.

After the pain interview, electrodes were placed on the stump. Initially the treatment was conducted with 16 electrodes in the TMC configuration (see Part I: Classification of Non-Weight-Bearing Lower-Limb Movements). However, after few treatment sessions, the muscles of the stump increased in size, producing stronger signals. Consequently, the electrodes were gradually reduced to eight (the subject preserved his ability to control the virtual environments). The location of the electrodes was determined by palpation while requesting the patient to move his phantom leg. **Figure 4** shows an example of the TMC configuration used.

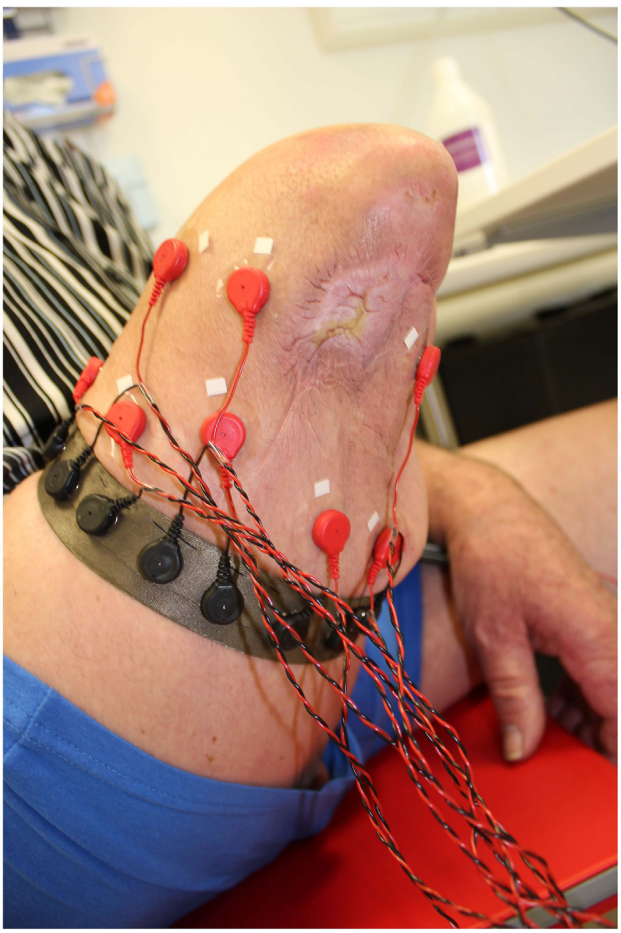

FIGURE 4 | Example of targeted monopolar configuration used for the *phantom motor execution* treatment of the patient with lower-limb amputation.

Different phantom movements (or set of movements) were exercised at an increasing level of difficulty as done in the upper limbs [see appendix of Ortiz-Catalan et al. (4) for details]. Myoelectric signals associated with the chosen set of movements were recorded to train the MPR system with LDA-OVO topology. The patient then practiced *PME* in virtual reality (VR), to later perform target achievement control (TAC) tests (30). The TAC test consists of executing the trained motions to control a virtual limb to match random target postures presented on the screen. The target postures reflected the previously trained 1 degree-of-freedom movements, as well as combinations of these to achieve multiple degrees of limb motions. The level of difficulty of the exercise depended on the number of movements trained, the type of movement, and if these were executed simultaneously. For example, distal movements are generally harder to control. On the other hand, consistent with our working hypothesis that *PME* reverts the central and peripheral maladaptive changes that took place following amputation, we aimed at exercising movements of the part of the phantom limb perceived as painful, which is commonly distal, as in the case of this patient.

Pain Assessment

The pain assessment interview was conducted at the beginning of each session and at 1, 3, and 6 months after the end of the treatment. We assessed changes in intensity, quality, and duration of PLP with a questionnaire derived from the Swedish version of the Short Form of the McGill Pain Questionnaire (SF-MPQ) (31) and study-specific questions. Specifically, the Numeric Rating Scale from 0 (no pain) to 10 (worst possible pain) was used to evaluate the intensity of pain at the moment of the interview. Moreover, quality and intensity of pain was assessed by the Pain Rating Index (PRI), as per SF-MPQ (32), and was calculated as the sum of the individual scores given to the pain descriptors. Furthermore, the time-varying pain profile of an average day was captured by a study-specific metric, the weighted pain distribution (WPD) (4–6), which required the patient to estimate the percentage of the time awake spent at each level of a 6-point scale (none to maximum, 0–5). The results of the questionnaire were then summarized in the WPD, which is the weighted sum of the pain scores. PLP location and length of the phantom limb were also monitored at each session. Finally, the patient was free to self-report comments regarding any aspect of the treatment, pain perception and quality of life.

RESULTS

Part I

Table 1 shows the results of the real-time tests as mean values and related SEs. For non-amputees, the real-time performance metrics and the offline accuracy are also presented in boxplots. In addition, data points representing the mean over the motions for amputees and non-amputees are plotted on top of the boxplots, and the pairs of the dependent samples are connected by lines (**Figure 5**). Finally, **Figure 6** shows the cumulative completion rate for both non-amputees and amputees, which represents the percentage of motions completed as a function of time.

The statistical testing for the comparison of TMC to TBC did not reveal any significant differences in the metrics for evaluating the performance in real time (completion percentage: $p = 0.37$; selection time: $p = 0.43$; real-time accuracy: $p = 0.31$; completion time: $p = 0.43$) or offline (offline accuracy: $p = 0.68$). Nevertheless, TBC performed better in the majority of the cases when considering the pairs between the two samples (data points connected by lines). A larger sample size could have likely revealed a significant difference.

In comparing UMC (eight channels) to TBC, a significant effect was found for the completion percentage ($p = 0.002$), while the remaining metrics presented no significant differences (selection time: $p = 1$; real-time accuracy: $p = 0.81$; completion time: $p = 0.58$; offline accuracy: $p = 0.73$). Similarly, the comparison between UMC and TMC yielded a significant difference in the completion percentage ($p = 0.002$), but not in the other metrics (selection time: $p = 0.39$; real-time accuracy: $p = 0.13$; completion time: $p = 0.13$; offline accuracy: $p = 0.48$).

Finally, the investigation conducted of UMC revealed that 16 channels did not have any improvement over the performance of the electrode configuration with just 8 channels, and no significant differences were found (completion percentage: $p = 0.56$; selection time: $p = 0.56$; offline accuracy: $p = 0.68$), even though real-time accuracy and completion time were better with 8 channels, as seen from the low p-value and the pairwise visual inspection in **Figure 6** (real-time accuracy: $p = 0.03$; completion time: $p = 0.03$).

Part II

The interventions took place between January 28, 2016 and April 19, 2016. The patient was initially able to control proximal movements (knee flexion/extension, hip rotation medial/lateral) in only 1 degree of freedom. By the end of the treatment, the patient

TABLE 1 | Performance metric mean values (SE) for each configuration: targeted monopolar configuration (TMC), targeted bipolar configuration (TBC), untargeted monopolar configuration with 8 channels (UMC-8 ch), and untargeted monopolar configuration with 16 channels (UMC-16 ch).

Performance metric	TMC		TBC		UMC-8 ch		UMC-16 ch	
	Amputee ($n = 2$)	Healthy ($n = 6$)	Amputee ($n = 2$)	Healthy ($n = 6$)	Amputee ($n = 2$)	Healthy ($n = 6$)	Amputee ($n = 2$)	Healthy ($n = 6$)
Completion rate %	75.0 (4.2)	79.8 (2.1)	80.2 (7.3)	83.7 (5.3)	79.1 (16.6)	91.3 (4.1)	69.8 (13.5)	87.5 (6.0)
Real-time accuracy %	81.7 (6.1)	81.5 (3.0)	86.9 (1.6)	84.6 (2.9)	86.0 (1.6)	84.7 (2.3)	83.9 (2.3)	81.4 (1.1)
Completion times	5.15 (0.35)	5.15 (0.12)	4.75 (0.13)	4.95 (0.12)	4.86 (0.14)	4.88 (0.08)	4.91 (0.12)	5.13 (0.05)
Selection times	0.84 (0.21)	0.77 (0.05)	0.59 (0.14)	0.72 (0.12)	0.83 (0.38)	0.69 (0.10)	1.25 (0.49)	0.88 (0.05)

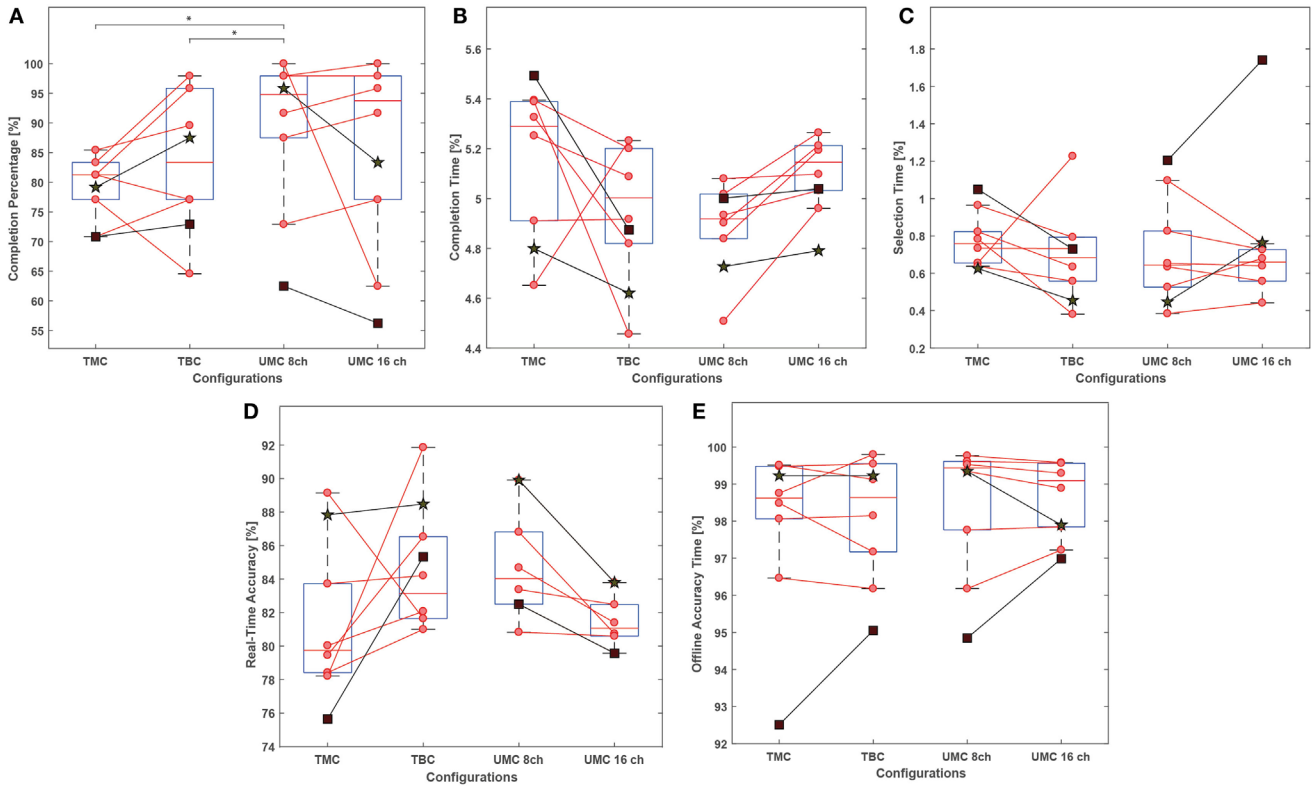

FIGURE 5 | Box plots presenting the results of the comparison of the three electrode configurations in terms of real-time metrics relative [i.e., **(A)** completion percentage, **(B)** completion time, **(C)** selection time, **(D)** real-time accuracy] and **(E)** offline accuracy. The boxplots represent only the data relative to non-amputated subjects. The line in the center of the boxes indicates the location of the median, the upper edge indicates the third quartile, the bottom edge represents the first quartile, and the whiskers indicate the data range. Along with every boxplot, it is possible to the mean value for each subject. Red dots represent non-amputees, while the square and a star marker represent the data points for the transtibial and the transfemoral amputee subject, respectively. Statistical significance ($p < 0.05$) is marked by the *.

had acquired control over the entire lower limb, including toes, and was able to exercise up to 4 degrees of freedom within the same session (Video S1 in Supplementary Material). Between the first and the last treatment session, an overall reduction of PLP intensity was measured by all metrics. PLP intensity decreased by 2 points on the NRS scale (from 4 to 2, 50%) and by 22 points in PRI (32 to 10, 68%) (**Figure 7**). A positive change was also reported in the time-varying profile of PLP, in which the WPD decreased by 1.8 points (from 3.2 to 1.4, 57%) by the last treatment session (**Figure 8**). The progress in pain reduction, presented as distribution of pain over time, is presented in **Figure 9,** and the estimated time slept is presented in **Figure 10**. In particular, the higher-intensity PLP (pain levels of 4 and 5), usually present in the evening and at night, reduced considerably over time. This was accompanied by an increase in length and quality of sleep from 2 h per night with interruptions to 7 h without interruptions. The pain location remained constant throughout the entire treatment period (in the foot), and the phantom limb maintained the same dimensions it had at the beginning of the treatment, thus being of the same length as the normal leg. The patient noted an improvement in quality of life since the start of the treatment, with less tiredness, improved mood, and regained ability to drive for long distances (>200 km at a time, which was not possible before). Moreover, both family and patient observed a reduction in the use of the neurostimulator during the day.

From **Figures 7–10**, it is also possible to see the profile of PLP after the end of the treatment, as recorded at the follow-up interviews 1, 3, and 6 months after. The positive effects of the treatment were retained at the first and second follow-up interviews but had almost vanished by the sixth month.

DISCUSSION

The aim of this study was twofold. First, we wanted to investigate the performance of two alternative electrode configurations to conventional bipolar targeted recordings in terms of real-time metrics. Second, we evaluated *PME* as a treatment of PLP on lower-limb amputations in a chronic intractable case.

In the first part of this article, we showed that classification is possible similarly in all of the three configurations. Looking at the comparison between TMC and TBC in the boxplots of **Figure 5**, the latter performed better in most cases. A possible explanation of this result is that the distance between the electrodes, and the

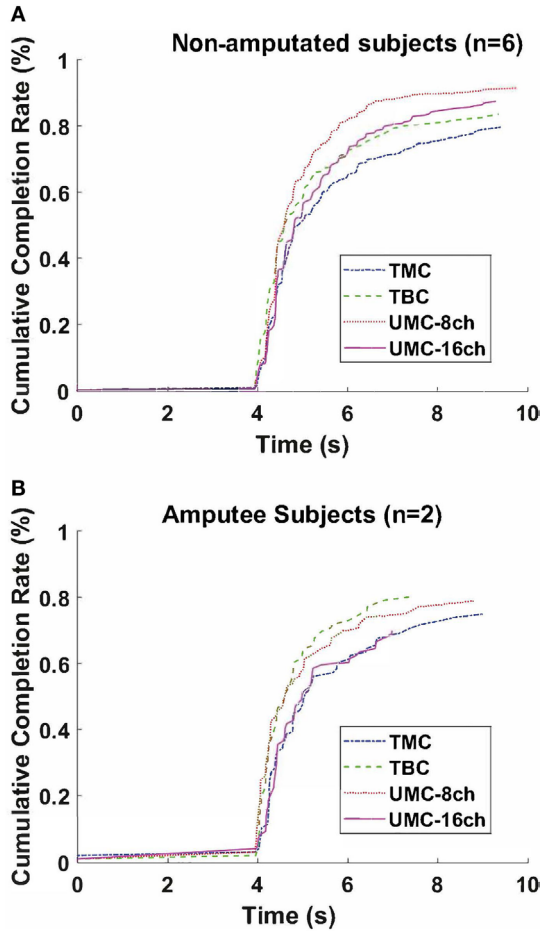

FIGURE 6 | Cumulative completion rate for **(A)** non-amputated and **(B)** amputated subjects.

CCE in TMC, is generally larger than the inter-electrode distance for TBC. This could result in an increase of crosstalk picked up by the electrodes and CCE, yielding lower SNR, as our previous study showed (23). Conversely, the distance between the electrodes and the CCE in the UMC was reduced, possibly rendering fewer disturbances in the signals, thereby explaining the better performance.

It is worth noticing that the UMC with 16 channels did not outperform the same configuration with just 8 channels. On the contrary, it might appear that, when considering real-time accuracy and completion time, fewer channels improved the performance.

Besides real-time performance of the classifier, there are secondary factors that can be taken into account to determine which electrode placement method should be preferred for a clinical application. First, TBC might not be an option when dealing with patients with short stumps, as not all the muscles required for targeted configurations might be available. Second, the targeted electrode placement can be difficult and time consuming because of the difficulty of identifying the correct muscles, due to excessive soft tissue, weakness, or muscle relocation, even when the muscles are available. Third, the use of bipolar electrodes requires parallel alignment to the muscle fibers for optimal recordings (33), as well as avoiding innervation zones (34). Parallel alignment in differential measurements is recommended because this is the direction of the propagation of the action potential. However, this alignment is difficult to achieve in muscle fibers forming a pennation angle (such as the quadriceps). Altogether, sEMG signal acquisition in the lower limbs could be facilitated by placing the electrodes in monopolar configurations (UMC and TMC). This configuration is insensitive to the fiber orientation and position of the electrode, with respect to the innervation zone. Moreover, we show that it is not necessary to target all the superficial muscles of the thigh, even when available. UMC yielded real-time classification accuracy comparable to the targeted configurations (TMC and TBC). However, optimizing the targeted electrode placement by identifying the active areas of the stump muscles can improve the quality of the MPR in amputee subjects.

Altogether, UMC or TMC, with CCE made of conductive fabric, was beneficial for implementing a rehabilitation system. In addition to faster and easier electrode placement, such configurations also need only half the pre-gelled adhesive electrodes normally used in a bipolar configuration. This means an economic advantage, in addition to reducing material waste.

Moreover, the use of the CCE of conductive fabric opens possibilities for developing solutions made entirely of wearable smart textiles, which would allow patients to easily take them on and off. In addition, a textile solution could be reused and easily be adapted for different anatomies without changes in the design (35).

The second part of the paper was dedicated to evaluating *PME* as a strategy to treat PLP in a subject with lower-limb amputation. In accordance with previous studies on upper limbs (4–6), improvement was found in all the metrics used for pain evaluation following treatment by *PME*. Conversely, PLP was not eliminated completely, despite the fact that the intervention took place over a longer period of time and follow-up interviews revealed that the positive effects almost vanished within 6 months, as opposed to what was demonstrated in the previous clinical trial. Overall, this might indicate that more sessions are required in case of PLP in the lower extremities, or that the contribution of augmented reality could induce more rapid, longer-lasting changes.

Nevertheless, we showed that the realistic visual feedback induced by augmented reality was not essential to obtain pain reduction *via PME* treatment, raising doubts as to whether or not, a more realistic visual illusion concerning the virtual limb is necessary to mediate the perception of PLP. Our work and others suggest a relationship between the ability to control movements of the phantom limb and PLP, and therefore we cannot exclude that pain relief could be achieved just by training phantom mobility without appropriate visual feedback. Our previous studies, together with the current one, are limited in this sense due to the lack of an appropriate control group, and additional investigations aimed at unveiling these aspects are required.

Although not quantified, we observed morphological changes in the stump related to regained muscular mass. These changes were accompanied by improvement in voluntary control of the phantom limb, also not recorded by any direct measure, but

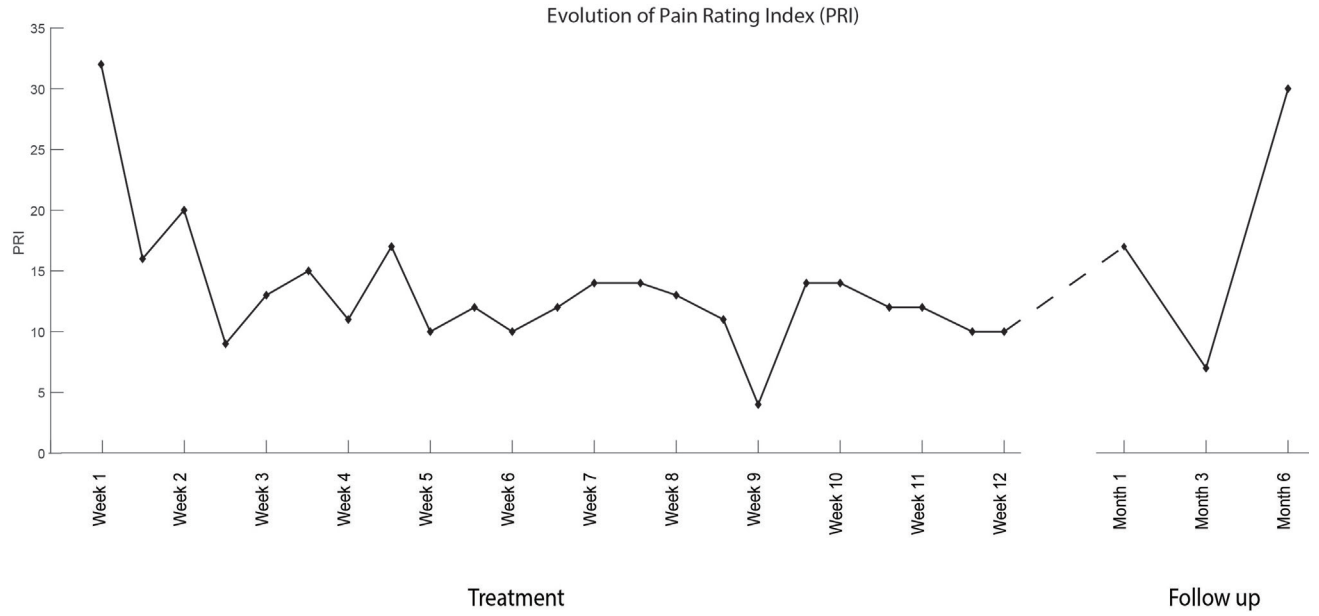

FIGURE 7 | Evolution of the Pain Rating Index (PRI) over the course of the treatment and in the follow-up period (6 months). The PRI is calculated as the sum of the scores (0–5) assigned to the pain descriptors of the Short Form of the McGill Pain Questionnaire (SF-MPQ). The SF-MPQ was administered at the beginning of each treatment session twice per week (left hand side of the dashed line) and at 1, 3, and 6-month follow-up (right hand side of the dashed line).

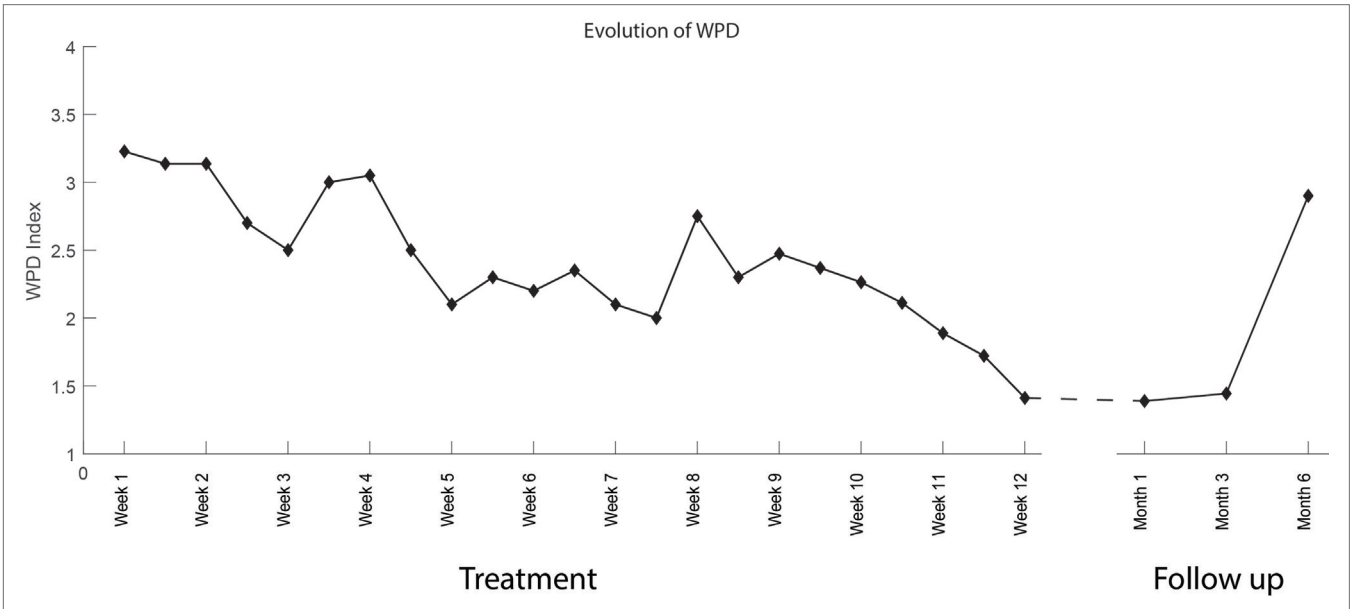

FIGURE 8 | Graph representing the value of the Weighted Pain Distribution (WPD) throughout the 23 treatment sessions and at 1, 3 and 6-month follow-up (right hand side of the dashed line). The WPD is calculated as the sum of the scores (0–5) weighted on the total time spent awake.

clearly indicated by the ability to control an increasing number of degrees of freedom of the virtual limb. It is possible that structural alteration of the stump was accompanied by functional and neurophysiological variations, accounting for the effects that we observed on PLP. In the future, studies should quantify morphological changes in the stump, improvements in phantom motor control, alteration of sensorimotor cortical maps, and how these relate to PLP.

Finally, the use of a CCE for monopolar recording may allow for faster electrode placement, which means that more time can

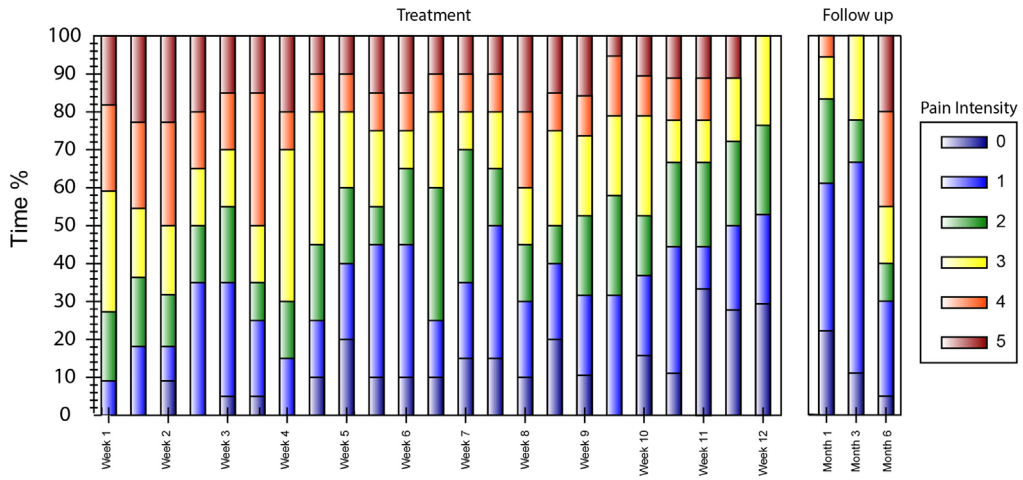

FIGURE 9 | Weighted pain distribution (WPD) bar graph. Each bar represents a treatment session or a follow-up interview. The pain rating is from 0 to 5 where 5 (red) is the worst possible pain.

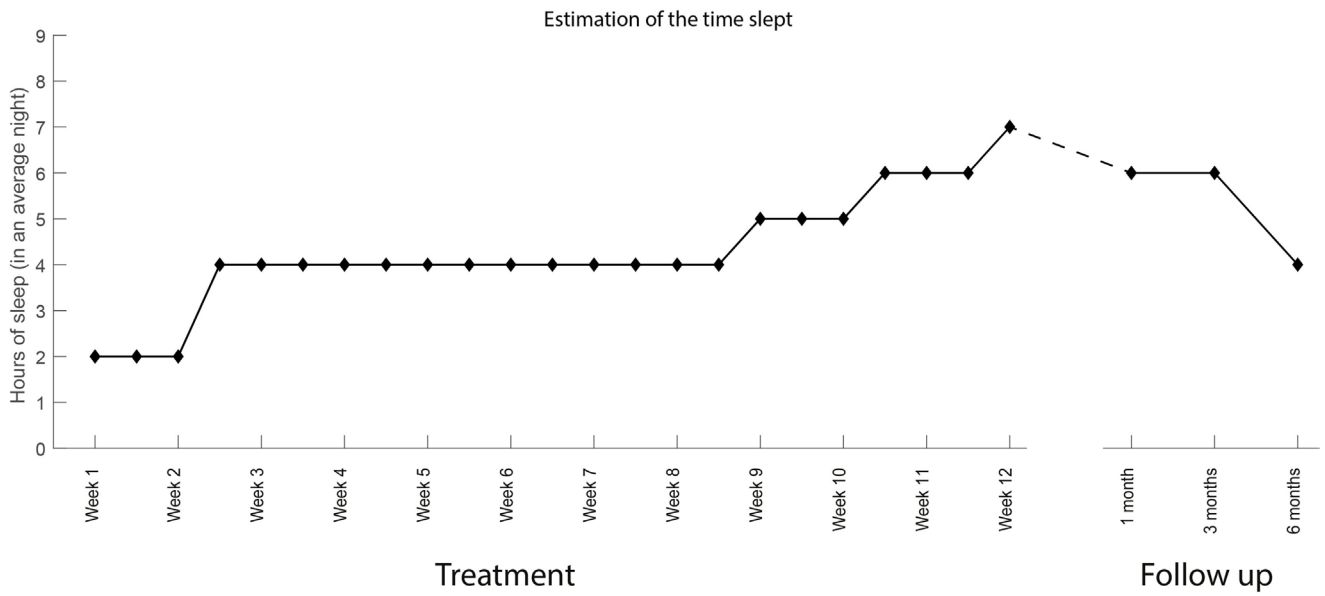

FIGURE 10 | Time slept as estimated by the subject over the course of the treatment and during the follow-up period.

be spent in the treatment rather than in the setup. Moreover, using the monopolar configuration also implies that roughly 200 Ag/AgCl pre-gelled electrodes were spared in this particular case study.

CONCLUSION

In the first part of this work, we demonstrate the possibility to use different techniques to acquire sEMG signals suitable for successful MPR of lower-limb movements in non-weight-bearing conditions. We concluded that monopolar recordings, enabled by a single differential electrode around the leg, seem a viable solution for a rehabilitative application. Future work will focus on further development of the system to make it more user-friendly.

In the second part, we investigated the efficacy PME in reducing chronic, intractable PLP on a subject with lower-limb amputation. The results were limited to one subject but were positive and put forward the need to investigate in a wider population to determine if PME, facilitated by MPR and VR, can effectively reduce PLP in the lower limb.

In conclusion, the results of this research give us grounds to continue the work on our long-term goal of implementing a system for treating PLP based on *PME* for subjects with both upper- and lower-limb amputations.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the *Handbook for Good Clinical Research Practice*, by the World Health Organization. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The regional ethical committee of Västra Götalandsregionen approved this study.

AUTHOR CONTRIBUTIONS

EL and MO-C designed the studies and the electrode configurations. EL performed the literature review, conducted the study on the electrode configurations, performed the interventions for the *phantom motor execution* treatment, analyzed the results, and drafted the manuscript. MO-C developed the motion prediction technology (software). EM designed and developed the hardware. MO-C and BH supervised this research and revised the manuscript. All the authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00470/full#supplementary-material.

VIDEO S1 | The subject performing the target achievement control (TAC) test with 4° of freedom during the phantom motor execution (PME) treatment.

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Conflict of Interest Statement: MO-C was partially funded by Integrum AB, a for-profit organization that might commercialize an improved version of the technology here described. The core technology used in this study has been made freely available as open source by MO-C and EM (machine learning, virtual reality, and electronics). EL, EM, and BH declare no competing interests.

PAPER B

Phantom Motor Execution as a treatment for Phantom Limb Pain: Protocol of an international, double-blind, randomized, controlled clinical trial

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BMJ Open

Phantom motor execution as a treatment for phantom limb pain: protocol of an international, double-blind, randomised controlled clinical trial

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ABSTRACT

Introduction Phantom limb pain (PLP) is a chronic condition that can greatly diminish quality of life. Control over the phantom limb and exercise of such control have been hypothesised to reverse maladaptive brain changes correlated to PLP. Preliminary investigations have shown that decoding motor volition using myoelectric pattern recognition, while providing real-time feedback via virtual and augmented reality (VR-AR), facilitates phantom motor execution (PME) and reduces PLP. Here we present the study protocol for an international (seven countries), multicentre (nine clinics), double-blind, randomised controlled clinical trial to assess the effectiveness of PME in alleviating PLP.

Methods and analysis Sixty-seven subjects suffering from PLP in upper or lower limbs are randomly assigned to PME or phantom motor imagery (PMI) interventions. Subjects allocated to either treatment receive 15 interventions and are exposed to the same VR-AR environments using the same device. The only difference between interventions is whether phantom movements are actually performed (PME) or just imagined (PMI). Complete evaluations are conducted at baseline and at intervention completion, as well as 1, 3 and 6 months later using an intention-to-treat (ITT) approach. Changes in PLP measured using the Pain Rating Index between the first and last session are the primary measure of efficacy. Secondary outcomes include: frequency, duration, quality of pain, intrusion of pain in activities of daily living and sleep, disability associated to pain, pain self-efficacy, frequency of depressed mood, presence of catastrophising thinking, health-related quality of life and clinically significant change as patient's own impression. Follow-up interviews are conducted up to 6 months after the treatment.

Ethics and dissemination The study is performed in agreement with the Declaration of Helsinki and under approval by the governing ethical committees of each participating clinic. The results will be published according to the Consolidated Standards of Reporting Trials guidelines in a peer-reviewed journal.

Trial registration number NCT03112928; Pre-results.

Strengths and limitations of this study

- This study involves a suitable number of participants (>60) to provide the power necessary for meaningful conclusions.
- This study is double-blinded, randomised controlled clinical trial, conducted in geographically different locations and involves subjects with both upper and lower limb amputations, thus enhancing generalisability.
- The choice of the comparator allows controlling in a stringent manner for the effect of the key factor hypothesised as the cause of pain reduction, namely, the execution of phantom limb movements.
- Treatment is limited to 15 sessions, which might not be enough to alleviate pain in all participants.
- The nature of the experimental treatment (phantom motor execution) does not allow inclusion of individuals from which myoelectric signals cannot be recorded from the muscles in their residual limbs.

INTRODUCTION

Phantom limb pain (PLP) is a chronic condition commonly suffered by amputees.[1 2] Although more than 60 different treatments to alleviate PLP have been described in the literature,[3] controlled clinical trials on such treatments are scarce and tend to be of poor quality.[4] The clinical investigation presented in this protocol aims to evaluate the efficacy of phantom motor execution (PME) in reducing PLP in an international, multicentre, double-blind, randomised controlled clinical (RCT) trial. PME is accomplished by using a system (Neuromotus, Integrum AB, Sweden) that employs myoelectric pattern recognition to predict motor volition (movements of the phantom limb) while providing real-time feedback to the patient in virtual and augmented reality (VR/AR) environments.

This technology allows the application of serious gaming in the therapy. PME is a non-invasive, non-pharmacological and engaging treatment with no identified side effects at present.[5 6]

The effectiveness of PME was initially explored in a single upper limb amputee, with satisfactory results reported.[5] Prior to the pilot study, the patient had shown resistance to a variety of treatments for 48 years (including mirror therapy). After PME, the sustained level of pain reported by the patient was gradually reduced to pain-free periods. He and his family also reported less intrusion of PLP in sleep and activities of daily living (ADLs). Finally, the patient also acquired the ability to freely move his phantom arm and hand, consistent with a recent study by Raffin and colleagues[7] where they found that reduced capability of phantom movement was correlated with more severe PLP.

In the light of the findings in the case study, a non-randomised clinical investigation on PME was conducted in subjects with chronic intractable upper limb PLP.[6] Fourteen patients, for whom conventional PLP treatments failed and who suffered from PLP for an average of 10 years, received 12 treatment sessions of PME, each of 1.5-hour duration. At the end of the treatment period, patients showed statistically and clinically significant improvements (approximately 50% reduction of PLP). Intrusion of PLP during sleep and ADL was also reduced by a similar degree. These improvements were still present up to 6 months' post-treatment.[6] More recently, PME was also demonstrated to be a viable treatment for PLP in lower limb amputations.[8]

Strong evidence shows that PLP is related to neuroplastic changes in the primary somatosensory cortex, suggesting that central maladaptive plasticity is responsible for its maintenance. Neuroplasticity-based approaches for the relief of PLP, such as motor imagery and mirror therapy, ultimately aim to regain brain circuitry from pain processing. Nonetheless, these approaches have been shown to be limited in their effectiveness.

Although the practice of motor imagery has been shown to normalise previously altered cortical maps and reduce PLP,[9] evidence from randomised clinical studies has also suggested that it can increase pain.[10] These seemingly contradictory findings suggest that motor imagery should not be used alone but combined with other interventions, such as graded motor imagery[11] or mirror therapy.[12]

Mirror therapy has demonstrated higher effectiveness than motor imagery in reducing pain[10]; however, it still cannot ensure that the patient performs movements with the phantom limb. For instance, it is enough for the patient to move their healthy arm to produce movement in the reflected limb. Whether a patient is actually engaging in execution of phantom limb movements is unknown. PME overcomes some of the methodological limitations of previous treatments by ensuring that central and peripheral mechanisms in motor control are activated during therapy.

Table 1 List of the investigational sites, divided by countries taking part to the international, multicentre randomised clinical trial

Country	Investigational site
Sweden	Sahlgrenska University Hospital, Gothenburg Örebro University Hospital, Örebro Rehabcenter Sfären, Bräcke Diakoni, Stockholm
Slovenia	University Rehabilitation Institute, Ljubljana
Belgium	Fysische Geneeskunde en Revalidatie University Hospital Gent, Gent
The Netherlands	Department of Rehabilitation Medicine, University Medical Centre Groningen, Groningen
Canada	Institute of Biomedical Engineering, University of New Brunswick, New Brunswick
Ireland	Centre for Pain Research, National University of Ireland, Galway
Germany	Department of Psychosomatic Medicine and Psychotherapy, LWL University Hospital, Ruhr-University Bochum, Bochum

STUDY OBJECTIVE

This paper presents the study protocol for a RCT in which upper and lower limb amputees are treated. The investigation primarily aims at assessing the efficacy of PME aided by myoelectric pattern recognition, VR/AR and serious gaming to reduce PLP. In order to isolate the contribution of PME in alleviating PLP over potential placebo effects, phantom motor imagery (PMI) is used in this study as an active control treatment.

The working hypothesis of PME is that execution of phantom limb movements would exploit competitive neuroplasticity and provide a more integral normalisation of cortical, subcortical and spinal circuits compared with interventions that do not enable integration of sensory and motor information. Therefore, in this superiority trial, we hypothesise that the participants receiving the experimental treatment (PME) to obtain a larger reduction in PLP levels than those randomised to the control treatment.

TRIAL DESIGN

This clinical study is an international, multicentre, double-blind, randomised controlled trial. The study takes place in seven counties and involves nine clinics, which are listed in table 1. Participants are randomly assigned to receive either the experimental or the control treatment in a 2:1 allocation ratio. The choice of the allocation ration was made in order to collect more data on the intervention of interest. Each patient is followed up for a period of 6 months, at the end of which they are given the choice to undergo the alternative treatment. The total duration of the study is expected to be approximately 3 years.

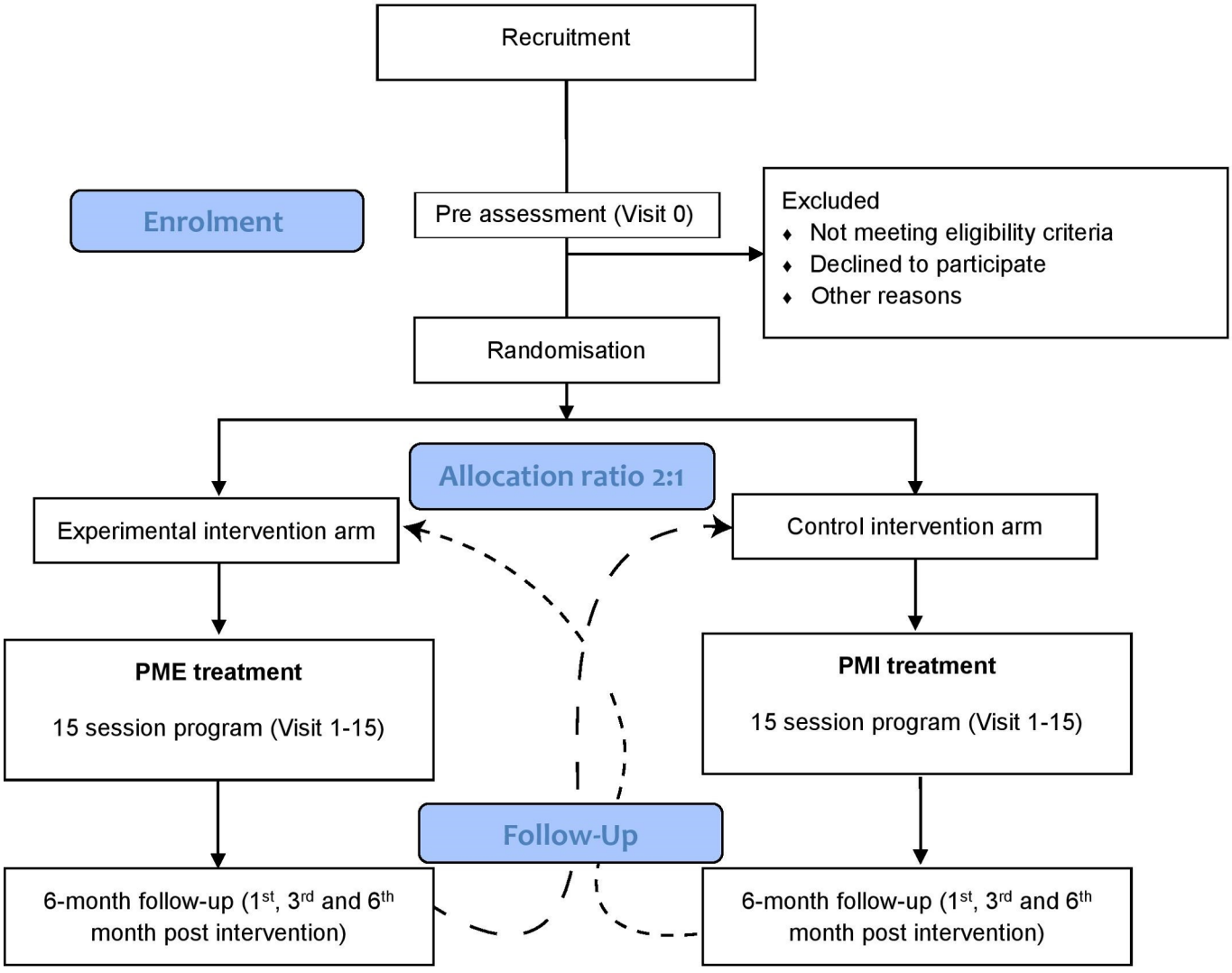

Figure 1 Flow diagram for the randomised controlled clinical trial. At least 67 patients are recruited and randomly allocated to either phantom motor execution (PME) or phantom motor imagery (PMI) interventions in allocation ratio 2:1. Following the completion of the treatment protocol and wash-out period of 6 months, it is possible for the patient to cross over to the parallel interventional arm, according to their will.

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

A procedural overview of the trial is provided by the flow diagram of figure 1. Recruitment of the participants is conducted via advertisements at local investigation clinics, on social media and in local newspapers. People who are interested in taking part in the trial are invited to contact the principal investigator of the site, or a person appointed by the principal investigator, via phone or email.

Eligibility criteria

Interested people are invited to a preassessment visit (visit 0). On this occasion, the therapist (clinical investigator) explains the study in detail and answers all the questions that might arise. Afterwards, the participants are asked to provide written informed consent (see supplementary appendix A). If consent is granted, eligibility to the study is assessed according to the criteria presented below:

- The participants must be older than 18 years with chronic PLP.
- Participants must have chronic PLP—at least 6 months should have passed since amputation. Participants with acute PLP are non-eligible.
- In case of pharmacological treatments, the dosage must have been stable for the previous month.
- Any previous PLP treatments must have terminated at least 3 months prior to entering the study.
- Any pain reduction potentially attributable to previous PLP treatments must have occurred at least 3 months prior to entering the study.
- Voluntary control over at least a portion of biceps and triceps muscles in case of upper limb amputation or quadriceps and hamstrings in case of lower limb amputation.
- Stable prosthetic situation (ie, satisfaction with the fitting of the prosthesis) or being a non-user.

- The subject should not have a cognitive impairment that prevents them from following instructions.
- No abundant soft tissue on the stump that prevents sufficient myoelectric signals from being recorded.
- No presence of pain >2 on Numerical Rating Scale (NRS) on contact with the skin or muscle contraction in the stump.
- The PLP must not be aggravated (NRS >4) by the execution or imagination of phantom movements.
- No condition associated with risk of poor protocol compliance.
- No injury, disease or addiction that would render the individual unsuitable for the trial.
- Pain Rating Index (PRI) >0 as assessed in the Questionnaire for Phantom Limb Pain (Q-PLP) at visit 0.

Concomitant medications

Any cointervention aiming to reduce PLP is prohibited during the trial. However, in the design of the trial, it is acknowledged that there is a large possibility for patients with PLP to be high consumers of analgesic medicines. Therefore, the use of concomitant medications is allowed provided that at the time of inclusion, the patient has stable consumption for at least 1 month before entering the study and any pain reduction potentially attributable to the drug occurred at least 3 months before entering the study. Intake of pain medication in patients who show considerable improvement can be gradually reduced at the discretion of the responsible physician, given that the patient is followed up regularly. Medication intake is thus monitored as an outcome variable called 'need of concomitant medication', which is used to describe and compare the amount of comedication in the treatment groups.

Interventions

All of the therapists at the clinics are introduced to the technology with at least one practical demonstration by the first (EL) and/or last author (MO-C). The therapists conduct the interventions independently, and periodically the first author monitors the correct execution of the protocol. Participants in both intervention groups receive 15 treatment sessions of 2 hours' duration, including system setup and a blinded outcome assessment. The frequency of the sessions is chosen by the participant and can be once, twice (advised frequency) or five times per week, yielding a total patient duration that ranges between 28 and 40 weeks. Both treatment groups use the same device and setup, which are sketched in figure 2. The only difference between the two groups is the type of interaction with the virtual environments (active: motor execution; or passive: motor imagery). Allocated interventions for a given trial participant cannot be modified. Dates of the treatment sessions are recorded.

Experimental treatment

In the PME intervention, motor volition is decoded by interpreting the signals from the stump muscles via myoelectric pattern recognition.[13 14] The decoded movement is visualised in the virtual environments (ie, virtual limb or serious gaming). The end result is that the user, by training with the system, can achieve control over the virtual environments by performing phantom limb movements associated with kinetic sensations analogous to the ones pertaining to the limb prior to amputation.

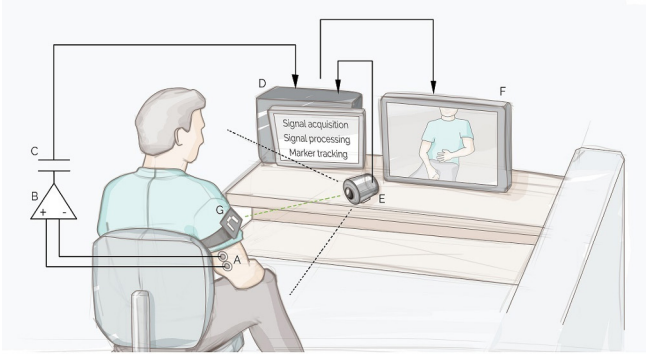

Figure 2 Schematic illustration of the clinical investigation device with all its components. Myoelectric signals are acquired though surface electrodes (A) by a myoelectric amplifier (B), electrically isolated (C). The signals are then processed by the software installed on the computer (D). The camera (E) films the participant and the recorded image is displayed on the monitor (F) with a virtual limb superimposed where the marker (G) is detected. Figure courtesy of Jason Millenaar.

A treatment session consists of the following steps:

1. Placement of the electrodes and fiducial marker.
2. Treatment cycles
   a. Recording session.
   b. Practice of PME with VR/AR.
   c. Serious gaming using phantom movements.
   d. Practice of PME by matching random target postures of a virtual arm in VR (TAC Test[15]).
3. Pain evaluation (Q-PLP; see Outcomes section).

Different treatment cycles (step 2) are repeated during a treatment session in order to execute various phantom limb movements or combinations of movements. The level of difficulty gradually increases during the treatment phase from 1 to 5 by adding df to be trained within the same treatment cycle. In this context, a df is any pair of movements performing opposite actions such as opening and closing of the hand or extension and flexion of the knee.

Clinicians are instructed to advance the level of difficulty once the previous level is accomplished successfully and revert to the previous level if the patient shows considerable difficulty accomplishing the tasks. More details on the acquisition of myoelectric signals, prediction of motor volition, the various parts of the treatment session and the different levels of difficulty are presented in online supplementary appendix B.

Control treatment

In the control treatment (PMI), patients are not allowed to produce/execute phantom movements, but must imagine performing such movements while observing them

executed autonomously by the VR/AR environments. The device is identical to the one used in the experimental treatment, but here the myoelectric signals are used to monitor that the patient does not produce muscular contractions, rather than decoding motor volition.

The control treatment session is conducted using the same stepwise procedure as the experimental group with the addition of a calibration step at the beginning of the treatment cycle. Calibration is necessary to set the threshold for myoelectric signals above, which the system alerts the user that a muscular contraction is performed. As in PME, the treatment cycle is repeated for different imaginary phantom limb movements or a set of imaginary movements following the same levels of difficulty. In the game format, the participants control the game using the keyboard with an able limb. Bilateral upper limb amputees use a joystick with any able limb. Details on the methods are presented in online supplementary appendix B.

Withdrawal or termination of individual participants

Participants are free to withdraw from participation in the study at any time on request. An investigator may terminate participation in the study if:

- Any clinical adverse event, clinical abnormality or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant no longer meets the eligibility criteria because of a condition newly developed or not previously recognised.

The main analysis will be conducted using the intention-to-treat (ITT) methodology. Missing data due to withdrawal or termination will be imputed using the 'last observation carried forward' method. From previous studies, the dropout rate is estimated at approximately 10%, and this was taken into account for the calculation of the sample size.

Outcomes

Outcomes will be evaluated at every treatment session and three follow-up assessments at 1, 3 and 6 months' post-treatment. The outcomes are measured by the evaluators following the participant treatment schedule presented in table 2.

Primary outcome measure

The primary outcome of the study is the change in PLP intensity measured by the difference in PRI between baseline (visit 0) and at the post-treatment assessment (visit 15). The PRI is computed as the sum of the scores for all descriptors of the Short Form of the McGill Pain Questionnaire (SF-MPQ).[16] Within this study, the SF-MPQ is included in one more extensive survey named Questionnaire for Phantom Limb Pain, which is described below in the secondary outcome measures.

Secondary outcome measures

Secondary outcomes consider different aspects related to PLP such as pain frequency, pain duration, quality of pain, intrusion of pain in ADLs and sleep, disability associated with pain, pain self-efficacy, mood, presence of catastrophising thinking, health-related quality of life and the patient's own impression about the effect of treatment. The secondary outcome measures are:

Table 2 Summary of the different items (intervention, forms and questionnaires) to be completed at each evaluation appointment

Session	Summary of content
Visit 0	► Patient information (T). ► Study consent (T). ► Preassessment (T). ► Background information (T). ► Q-PLP (T). ► PDI (T). ► EQ5D-5L (T). ► PSEQ-2 (T). ► PCS-SF (T). ► PHQ-2 (T). ► EXPECT-SF (T).
Randomisation	
Visit 1	► Treatment session (T). ► Q-PLP (E). ► OAT (E). ► EXPECT-SF (E). ► HCCQ-SF (E).
Visits 2–14	► Treatment session (T). ► Q-PLP (E).
Visit 15	► Treatment session (T). ► Q-PLP (E). ► PDI (E). ► EQ5D-5L (E). ► PSEQ-2 (E). ► PCS-SF (E). ► PHQ-2 (E). ► PGIC (E). ► HCCQ-SF (E).
1-month follow-up 3-month follow-up 6-month follow-up	► Q-PLP (E). ► PDI (E). ► EQ5D-5L (E). ► PSEQ-2 (E). ► PCS-SF (E). ► PHQ-2 (E).

The letter in brackets indicates whether the therapist (T) or the evaluator (E) is responsible of conducting a particular item is EQ-5D-5L, EuroQol-5D-5L; EXPECT-SF, Expectations for Complementary and Alternative Medicine Treatments Short Form; HCCQ, Health Care Climate Questionnaire; OAT, Opinion About Treatment; PCS-SF, Pain Catastrophizing Scale Short Form; PDI, Pain Disability Index; PGIC, Patients' Global Impression of Change; PHQ-2, two-item Patient Health Questionnaire; PSEQ-2, two-item Pain Self-Efficacy Questionnaire; Q-PLP, Questionnaire for Phantom Limb Pain.

Pain Disability Index (PDI)

PDI, a seven-item questionnaire designed to investigate the extent to which chronic pain interferes with a person's ability to engage in various life activities.[17] An

overall PDI score is obtained by summing the numerical ratings of the questionnaire's single items.

Questionnaire for Phantom Limb Pain

The Q-PLP is a 16-item questionnaire based on a combination of the SF-MPQ[16] and study-specific questions use in previous studies.[5 6 8]. The part containing the SF-MPQ is used for the calculation of the PRI (primary outcome measure).

The Q-PLP assesses intensity, quality, duration and frequency of PLP using the following metrics: the numeric rating scale (scale range 0–10) to assess the intensity of pain at present; the weighted pain distribution (scale range 0–5) to capture the time-varying nature of chronic pain by adding the contributions of weighted portions of time spent in six pain levels (present pain intensity scale,[18]); and a study-specific descriptive scale of seven steps: 'never', 'once per month', 'once per week', 'few times per week', 'once per day', 'few times per day' and 'always' to measure the frequency of pain.

In addition, the Q-PLP is used to monitor the intensity of stump pain, phantom limb sensations, phantom motor ability, intrusion of PLP in ADLs and sleep, by one question each using a numeric rating scale. Changes in prosthetic hardware, medication, presence of telescoping (feeling that the phantom limb is gradually shortening over time) and location of pain are also monitored by the Q-PLP.

EuroQol-5D-5L (EQ-5D-5L)

The EQ-5D-5L is a standardised questionnaire used to investigate health-related quality of life, which is constituted by two components: health status and health evaluation.[19] Health status is measured in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) on a five-point scale (no problems, slight problems, moderate problems, severe problems and extreme problems). In the health evaluation part, the EQ Visual Analogue Scale records the respondent's health on a vertical VAS where the end points are labelled 'best imaginable health state' and 'worst imaginable health state'.

Pain Self-Efficacy Questionnaire (PSEQ-2)

The PSEQ-2 is a two-item questionnaire that measures pain self-efficacy, which is the belief held by people with chronic pain that they can carry out certain activities and enjoy life, despite experiencing pain.[20 21] The items of the questionnaire are rated on a numeric rating scale from 0 to 6.

Pain Catastrophizing Scale – 6 (PCS-6)

The PCS-6 is a six-item questionnaire that investigates catastrophising thinking in a range from 0 to 4.[22 23] Pain catastrophising denotes a negative cognitive-affective response to pain and is associated to increased pain severity, disability and depressive symptoms and is associated with poor adjustment to chronic pain.[24]

Patient Health Questionnaire-2 (PHQ-2)

The PHQ-2 is a screening instrument consisting of two items assessing the presence of a depressed mood and a loss of interest or pleasure in routine activities.[25 26] The items of the questionnaire are rated on a numerical scale from 0 to 3.

Patients' Global Impression of Change (PGIC)

The PGIC is a single question used to identify clinically significant change by rating the patient's belief about the efficacy of treatment on a seven-point scale, ranging from 'no change (or condition has got worse)' to 'a great deal better'.[27]

Additional measurements

Participants are asked to supply details regarding background information such as age, gender, height, weight, type and use of the prosthesis, level of embodiment of the prosthesis, onset of PLP, details about previous and ongoing intervention for PLP and side, level and date of amputation. Additionally, we also survey: patients' expectancy of benefit using the Expectations for Complementary and Alternative Medicine Treatments (EXPECT-SF)[28]; patients' judgement about the credibility of the treatment using the Opinion About Treatment (OAT)[29] and patients' perception of therapists' supportive behaviour using the short form of the six-item Health Care Climate Questionnaire (HCCQ).[30]

Sample size

The calculation of the sample size was based on our primary hypothesis and informed by our previous clinical trial with no control group.[6] In order to find a mean difference of 4 between the two randomised groups in the primary outcome measure (PRI), with power of 80% resulting from a two-sided Fisher's non-parametric permutation test at 5% significance level, is estimated that at least 60 participants are required. As a drop-out rate of 10% is expected, a total of 67 patients will be randomised.

METHODS: ASSIGNMENT OF INTERVENTION

Randomisation

Participants are assigned to the experimental or control group according to the optimal allocation scheme of minimisation, aimed at reducing the imbalance between the number of patients allocated to each treatment group. The randomisation proportion is 2:1, with twice as many subjects assigned to the experimental treatment. The allocation ratio was chosen to collect more information on important variables regarding the intervention of interest. The allocation aims to minimise the imbalance of the following factors:

- Level of amputation (upper and lower).
- Baseline PLP based on the NRS (low 1–4, and high 5–10).
- Investigation site (nine centres).

The minimisation process is conducted using the open-source desktop application MinimPy,[31] operated by the monitor of the clinical trial. Every time a research team at a particular investigational site recruits a new participant, they assess the person's eligibility for the study (visit 0). Afterwards, if the participant is deemed eligible, the research team sends the minimisation factors relative to the enrolled participant to the monitor, who runs the randomisation and informs the research team of the allocation.

Blinding

This investigation has been designed in such a way that participants of the two treatment groups use the same device under the same circumstances.

Even though the patients are necessarily aware of the treatment they are receiving, they do not have an expectation of superiority of the experimental over the control treatment (or vice versa), since the trial is framed as a comparison between two different interventions previously described in the literature. It is worth noting that the distinction between motor execution and motor imagery is often imperceptible, even for professionals in the field, who have often described voluntary movements of the missing limb as imaginary movements.[9 32–37] We take this fact as a corroborant of our assumption that there are no differences at baseline with respect to expectations and opinions about the assigned treatment among participants. Nevertheless, individuals' expectations regarding outcomes and credibility of the assigned treatment are assessed with the EXPECT-SF and the OAT questionnaires, respectively.

The nature of the investigation does not allow the masking of the treatment for the therapists. However, it is still important to check for possible differences between the two groups concerning the therapists' supportive behaviour. For this reason, the HCCQ, is included as a measure of the extent to which a healthcare provider (or the staff) interacts with their patient in a supportive manner.

The outcome assessments are conducted by independent persons who are blinded to the group allocation, making the trial double blind. In order to keep group allocation confidential, participants are requested prior to each assessment not to reveal allocation or therapy content to the evaluators.

The raw data resulting from the outcome assessment has the same structure for both interventions, making it impossible to tell the group assignment without being in possession of the documents containing links between participant's identity and their code number.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

The monitor of the study (EL) is in charge of overseeing the progress of the RCT and ensuring that it is conducted, recorded and reported in accordance with the protocol, Good Clinical Practice (GCP) and regulatory requirements.

The monitor supplies case report forms (CRFs), which are filled in by the evaluator at each site. The evaluator is responsible to document all data obtained during the study, which is identified by participant code number. This also applies to data for patients who, after having consented to participate, undergo the baseline examinations required for inclusion in the study, but who are not included. No items in the CRF are to be left unattended: if data are missing or are impossible to obtain, these should be documented as 'not available' (NA) and the reasons for missing data must be noted in the document.

All data are recorded and stored in digital form on encrypted electronic devices. Documents containing links between a participant's identity and their code number exist only in paper form and are kept in locked file cabinets with limited access at the investigation site where the participants have been treated. In accordance with the regulations issued by The Swedish Data Protection Authority, a personal register will be established.

The clinical investigators are responsible to probe, via discussion with the participant, for the occurrence of adverse events during each visit and record the information in the patient CRF. Adverse events must be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study device, or if unrelated, the cause. The investigator must report any reportable event to the monitor in acceptable timely conditions, but not later than three working days after the occurrence of the event.

The sponsor must report to the Medical Products Agency (Läkemedelsverket) any serious adverse event, which indicates an imminent risk of death, serious injury or serious illness and that requires prompt remedial action for other patients, users or other persons immediately, but not later than two working days after becoming aware of a new reportable event or of new information in relation to an already reported event.

Once all the data are collected, checked and corrected, the database is closed, and analyses performed. All data transfer, processing and analyses are done using depersonalised data, and all the data sets are protected by password. In order to promote data quality, the evaluators are trained on all the data collection and management procedures and are provided with written instructions by the first (EL) and last (MO-C) authors.

To incentivise the completion of the follow-up, the patients are given the choice to participate in these assessments at the clinic or via a phone interview with the evaluators. When possible, follow-up assessments are also conducted with participants that had discontinued the treatment or withdrew from the study.

Statistical methods

The main analysis will be performed in terms of change from baseline to the measurement at treatment completion using the intention to treat (ITT) population, namely all the participants enrolled into the study considered according to their intial allocation. Complementary

analyses will be performed on the per-protocol (PP) population with respect to the change from baseline to the follow-up assessments at 1, 3 and 6 months after completion. These complementary analyses will include also the data coming from patients that, after appropriate washout period to exclude carry-over, have crossed over to the alternative treatment. Both the ITT population and the PP population will be specified in detail at the Clean file meeting before the database lock and before breaking the code. The PP population will be restricted to the participants who successfully complete all 15 treatment sessions.

Suitable graphical and numerical summaries will be provided for all the variables measured and for corresponding changes in scores.

For the main unadjusted comparison between two groups, Fisher's non-parametric permutation test will be used for continuous variables, Mantel-Haenszel χ^2 test for ordered categorical variables, Fisher's exact test for dichotomous variables and Pearson's χ^2 test for non-ordered categorical variables. CIs at 95% for the mean differences between two groups will be given when appropriate. If differences exist between the two randomised groups between baseline variables that could influence the outcome variables, a complementary adjusted analysis will be performed for these baseline variables.

For adjusted comparison between two groups, analysis of covariance will be used for continuous outcome variables not obviously non-normally distributed with intervention/control as independent variable and all confounders as covariates.

For analysis of change within groups, Wilcoxon signed-rank test will be used for continuous variables and sign test for ordered categorical and dichotomous variables. A complementary mixed model analysis between the two treatments regarding the primary efficacy variable with centre as random effect will be used to correct for the centre-effect in the statistical models.

All correlations will be performed with Spearman's correlation coefficient. The distribution of continuous variables will be given as mean, SD, median, minimum and maximum, and distribution of categorical variables will be given as numbers and percentages. All statistical tests will be two sided and conducted at the 5% significance level. The theory of sequential multiple test procedures will be applied for the primary analysis and for secondary analyses. If a test gives a significant result at the 5% significance level, the total test mass will be transferred to the following number in the test sequence until a non-significant result is achieved. All these significant tests will be considered confirmative. A Statistical Analysis Plan will be written with all detailed statistical analyses specified.

Patient and public involvement

The design of the study was informed by the experience with our previous clinical investigation,[6] thanks to which patients' priorities, experience and preferences were identified and used for the development of the research question and outcome measures of the current RCT. The burden of the control intervention was assessed with a pilot study on volunteers with past experience with the experimental intervention.

Ethics and dissemination

Research ethics approval

There are no known risks associated with the experimental or control treatments, and clinically significant deterioration is rare. Possible individual benefits include reduced PLP, reduced disability associated with pain and improvement in various aspects related to quality of life. This trial has been approved by the governing ethical committees of each participating country. Important protocol modifications will be reported in a timely manner to all the relevant parties.

Access to data

The principal investigator, MO-C, has full access to all of the data in the study except the documents containing the link between patient's identity and their code number, which will be accessible only after the completion of the data analyses. MO-C takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dissemination policy

Regardless of the significance, direction or magnitude of effect, the consortium will publish the findings of this study in scientific, peer-reviewed journals and conferences following the Consolidated Standards of Reporting Trials guidelines. All the clinical investigators will author the scientific article reporting the results of the trial. Results will be also disseminated to all the participants of the study with a report. No professional writers external to the study will be used aside from conventional English proof reading. Access to the detailed clinical investigation plan, participant-level dataset and statistical code will be granted based on reasonable requests after the publication of the study.

Trial status

This clinical trial is currently in the participant enrolment phase. Fourteen patients have been randomised and are under treatment at November 2017. It is anticipated that full analysis will be finalised in April 2020.

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Contributors MO-C conceived the phantom motor execution treatment. MO-C and EL reviewed the literature and designed the study. All authors provided feedback on the design of the trial. BEM and MP assisted in the selection of psychological measure. LB-K and KK-O coordinated the ethical applications. EL and MO-C drafted the manuscript. All authors revised the study protocol and approved the final manuscript. MO-C is the coordinating investigator of the study and endpoint adjudication evaluator. EL is the monitor of the trial, independent from the sponsor, and responsible for data management. Each site is constituted by at least a principal investigator, a therapist and a blinded evaluator. Investigational sites are independent from each other and from the sponsor.

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Disclaimer Neither the sponsor nor the funders (Promobilia, VINNOVA, EGG) had a role in the design of the present protocol.

Competing interests The sponsor of this study (Integrum AB) is a for-profit organisation that might commercialise the device used in this study (phantom motor execution and phantom motor imagery). MO-C was partially funded by Integrum AB. The core technology used in this study has been made freely available as open source by MO-C (machine learning, virtual reality and electronics).

Patient consent Not required.

Ethics approval Regionala Etikprövningsnämnden i Göteborg.

Provenance and peer review Not commissioned; externally peer reviewed.

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PAPER C

Out of the Clinic, Into the Home: The In-Home Use of Phantom Motor Execution aided by Machine Learning and Augmented Reality for the treatment of Phantom Limb Pain

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CASE SERIES

Out of the Clinic, into the Home: The in-Home Use of Phantom Motor Execution Aided by Machine Learning and Augmented Reality for the Treatment of Phantom Limb Pain

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Purpose: Phantom motor execution (PME) facilitated by augmented/virtual reality (AR/VR) and serious gaming (SG) has been proposed as a treatment for phantom limb pain (PLP). Evidence of the efficacy of this approach was obtained through a clinical trial involving individuals with chronic intractable PLP affecting the upper limb, and further evidence is currently being sought with a multi-sited, international, double blind, randomized, controlled clinical trial in upper and lower limb amputees. All experiments have been conducted in a clinical setting supervised by a therapist. Here, we present a series of case studies (two upper and two lower limb amputees) on the use of PME as a self-treatment. We explore the benefits and the challenges encountered in translation from clinic to home use with a holistic, mixed-methods approach, employing both quantitative and qualitative methods from engineering, medical anthropology, and user interface design.

Patients and Methods: All patients were provided with and trained to use a myoelectric pattern recognition and AR/VR device for PME. Patients took these devices home and used them independently over 12 months.

Results: We found that patients were capable of conducting PME as a self-treatment and incorporated the device into their daily life routines. Use patterns and adherence to PME practice were not only driven by the presence of PLP but also influenced by patients' perceived need and social context. The main barriers to therapy adherence were time and availability of single-use electrodes, both of which could be resolved, or attenuated, by informed design considerations.

Conclusion: Our findings suggest that adherence to treatment, and thus related outcomes, could be further improved by considering disparate user types and their utilization patterns. Our study highlights the importance of understanding, from multiple disciplinary angles, the tight coupling and interplay between pain, perceived need, and use of medical devices in patient-initiated therapy.

Keywords: phantom limb pain, neuropathic pain, augmented reality, phantom motor execution, ethnography, user interaction design

Introduction

Phantom limb pain (PLP) has been defined by the International Association for the Study of Pain (IASP) based on its perceived location; the phantom limb (IASP global year against neuropathic pain (2014–2015)). However, phantom limb pain (hereafter referred to as PLP) has a complex etiology and thus can be elicited by different sources, such as nociceptive (neuromas) and/or neuropathic.[1] Promising results have recently been

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published using surgical innervations to address nociceptive sources (neuroma pain),[2,3] but neuropathic causes remain unresolved,[4] even by pharmacological interventions.[5] This work is focused on neuropathic PLP and a non-invasive, non-pharmacological method to treat it.

PLP has been hypothesized as arising from the stochastic entanglement of the pain neurosignature with impaired sensorimotor circuitry.[1] In accordance with the implications of this hypothesis, a myoelectric pattern recognition (MPR) device was developed to promote Phantom Motor Execution (PME) as a treatment for PLP. PME engages motor neural circuitry in the central and peripheral nervous systems, ultimately resulting in the activation of the musculature at the residual limb while attempting phantom movements. By extracting motor intention from the stump's muscular activity, one can provide patients with real-time feedback utilizing Augmented and Virtual Reality (AR/VR), as well as serious gaming (SG).[6]

Preliminary evidence of the efficacy of this approach was obtained through a clinical trial involving individuals with intractable PLP affecting the upper limb,[7] and further evidence is currently being sought with a multi-sited, international, double blind, randomized, controlled clinical trial with upper and lower limb amputees.[8] All these experiments have been conducted in a clinical setting supervised by a therapist. However, when considering how the reduction of PLP relates to acquisition and maintenance of motor skills of the phantom limb, the question naturally emerges as to whether this treatment approach could be self-administered at home. The learning of phantom motor skills requires practice and occasional rehearsal is likely necessary to maintain said skills. With this in mind, we deemed it sensible to explore the feasibility of embedding PME in patients' home environments and daily life.

Studies of prescribed home use therapies have suggested that approximately 65 percent of patients will be non-adherent to some degree, due to factors such as lifestyle changes, complexity of the prescribed regime, lack of ability to fit the regime into normal routines, and the patient's internal level of motivation to do the treatment.[9] We were interested in understanding how these extrinsic lifestyle and personal factors interact with the patient's perceived need for the treatment as governed by pain levels, producing particular patterns of use and adherence.

In this manuscript, we present a series of four case studies on the use of Phantom Motor Execution as a self-treatment strategy for PLP. These case reports, involving two transhumeral and two transfemoral amputees, describe these patient's experiences using the therapy in their homes. We aimed to explore the benefits and the translational challenges encountered in the transition from clinic to home use. We hypothesized that home therapy yields efficacious results in pain reduction comparable to findings observed in the clinic, with the advantages of independent, customizable, personalized use outside of the hospital, as patients adapt the therapy to their individual preferences and lifestyles. In developing a more holistic understanding of how patients use the device at home and motivate themselves to perform the therapy, design recommendations can be drawn for future development of at home-based therapy systems.

In this study, we employ a multidisciplinary approach, enlisting the methodical and analytical tools of a biomedical engineer, medical anthropologist, and user interface designer. We chose this approach to elucidate not only the technical and quantitative data surrounding patients' in-home use of the therapy, but also to understand qualitatively the patient's relationship with their device and therapy program and develop design requirements for future in-home device development. Medical anthropology is the study of how social, cultural, biological, and structural factors intersect and interact with people's experiences of health, illness, medical treatments, and differentially distributed access to well-being. The primary methodological tool of anthropology is ethnography – sustained, immersive, long-term exposure of the anthropologist to individual's lives and worlds – in the endeavor to get as close as possible to understanding their firsthand experiences, practices, and values. Medical anthropology thus has the potential to complement, deepen, and even sometimes challenge the study of medical interventions through a more holistic lens.

Our study engages ethnographic insights into the lives of patients, involvement of family members, and behavioral patterns surrounding therapy to contextualize the clinical and quantitative perspectives. This multidisciplinary approach allows us to identify patterns otherwise overlooked using one method alone, offering an expanded appreciation of the many interrelated variables (physical, social, and structural) that drive patient home therapy regimes. Our study thus offers a methodological example of how engineers can work alongside interaction designers and anthropologists to produce a more deeply situated understanding of medical device development, use and efficacy, with the final aim of bringing such a device into the hands of the patient.

Materials and Methods

Design

All patients were provided with and trained to use a MPR and AR/VR device in a laboratory and/or clinical setting. Patients then took these devices home and used them freely and independently over the course of 12 months. At the end of the treatment period, the research group interviewed the subjects in an in-home setting and gathered the training data stored by the training software. The study was approved by the Regional Ethical Review Board in Gothenburg and was carried out in accordance with the relevant guidelines and regulations. All subjects provided their written informed consent to take part in the study and its publication.

Participants

Four limb loss patients (2 upper and 2 lower limb amputees) participated in this study. In the following we describe their backgrounds and their introductions to PME treatment.

Subject 1

Subject 1 (S1) is a 77-year-old man (born in 1941) who underwent an acute transhumeral amputation over 50 years ago (1964) in a motor vehicle accident, at age 24. S1 suffered from incapacitating phantom limb pain soon after the amputation, which severely impacted his sleep, mood, and ability to work. S1 experienced limited but unsustained PLP relief from hypnosis and mirror therapy. S1 was the first patient to undergo the PME treatment in 2013, resulting in the relief of nearly 50 years of PLP.[6] S1 was also the first person to use the device in-home, outside the clinic or laboratory.

Subject 2

Subject 2 (S2) is a 56-year-old man who lost his arm in 2011 in a tractor accident. He developed phantom limb pain directly after the accident, which he described manifesting as his hand clenched tightly in a fist. In 2014, he commenced PME therapy joining the first clinical trial on PME.[7] S2 had consistently taken morphine since the accident to help manage his PLP. Before joining the clinical trial, he used to take morphine pills in combination with morphine plasters, however by the end of his participation in the clinical trial he abandoned the plasters. He noticed that the valence of his pain changes with the seasons, getting markedly worse during winter, and he is currently using oxynorm (5mg/daily) to supplement his pain management.

Subject 3

Subject 3 (S3) is a 72-year old man who lost his leg in 1985 in a tractor accident. For the first 19 years after his accident, he did not experience debilitating phantom limb pain. Yet in 2014 S3 started to experience "unbearable" pain. The patient subsequently took part in a study using PME in lower extremities, which resulted in a significant decrease in PLP.[10] Following sustained PME treatment, the patient reported that his pain has returned to the level it was 20 years ago, "a manageable place." S3's pain was reported as worst in the middle of the night, when nothing else can distract him. As his son described, "my father is incredibly active. When he is always moving his body, he can't feel the pain. He once told me he wished he could just keep busy working for 24 hrs straight."

Subject 4

Subject 4 (S4), at 28 years old, is the youngest and in-home PME and AR/VR device user, and the only female in this study. She is a transfemoral amputee who lost her leg in a motor vehicle accident in 2009, when she was 18 years old. S4's phantom limb pain began almost immediately after her amputation and was, as she describes, "excruciating". S4 was prescribed a heavy dosage of oxycodone to manage her pain. For nine years, she continued taking oxycodone pills consistently. The pill was the only thing that allowed her to sleep, to escape what she called a "gnawing, annoying, relentless" sensation. She did not pursue any other pain management treatments during this time but was troubled by the strength of the medication and its numbing effects. In 2017, S4 was trained in PME and the AR/VR device in lab settings, upon which she took the device home with her. She continued the treatment at home, allowing periods of complete cessation of oxycodone.

Intervention: Home Use System

The PME treatment facilitated by MPR, VR/AR, and SG has been extensively described previously for the upper limb[6,7] and for the lower limb.[10,11] The same treatment methods were employed in this study. Briefly, motion intent is inferred via MPR using myoelectric activity from the stump musculature. First, the MPR algorithm is trained by recording the myoelectric signals associated with the phantom motions to be exercised. Once the aimed motions are trained and thus recognized by the decoder, these can be used to command the following virtual environments:

1. A VR environment featuring a virtual limb that is freely controlled by the subject.
2. An AR environment to allow the subject to visualize themselves (in real-time) with a virtual arm/leg superimposed on their stump. The AR environment uses a conventional webcam which inputs a video feed that is analysed to track a fiducial marker, thus allowing the virtual limb to remain in the anatomically correct position while the subject moves.
3. A racing game (Trackmania Nations Forever, free version) controlled by the subject's limb movements.
4. Target Achievement Control (TAC) test initially introduced by Simon and colleagues[12] and used in this study as implemented in BioPatRec.[13] The test requires the subject to match target postures presented in random order on the screen. The subject attempts to match the posture by moving the virtual limb with accuracy (i.e. the target posture can be overshot) and within a 10-second interval.

A user-friendly system (software and hardware) was developed for independent use at home. The software included a pain survey to monitor the level of PLP based on the Short Form of the McGill Pain Questionnaire (SF-MPQ) since prior clinical evidence gathered from patients using our system indicated this metric as the most sensitive measure of changes in pain.[7] Although subjects in this study were free to use the system according to their needs and to best suit their lifestyles and schedules, the recommended regimen was two sessions per week for at least 90 mins of training (this regimen has demonstrated efficacious in our previous clinical experience). Patients were also asked to occasionally fill in the pain survey in order to monitor the long-term profile of their PLP.

Data Collection and Outcome Measures

Data concerning the use of the system was stored in the software and collected at the end of the one-year study period. We monitored the frequency of the sessions, number of recording session per session and number and type of motions per recording session. Data regarding pain was collected through the self-administered questionnaire included in the software, which reports dates and times. The subjects were instructed to fill in the questionnaire at the end of every training session. The outcome measures considered were:

- Treatment adherence: Monitored as the number of sessions carried out monthly.
- Session duration: Inferred from the timestamps of the recording sessions as the time elapsed between the first and last recording of the day. This time interval was then increased by the average time between two consecutive recording sessions in order to account for the time spent in virtual environments by training with the last recording session.
- Pain Rating Index: Computed as the sum of the scores for all descriptors of the Short Form of the McGill Pain Questionnaire (SF-MPQ).[14] The SF-MPQ consists of 15 pain descriptors rated on a 4-point scale from 0 to 3. The range of the PRI is therefore 0 to 45.

Due to the small sample size and variations in patients' home situations, lifestyles and personal preferences, this study was not conducted as a clinical trial, nor does it draw conclusions of statistical significance. Rather, it is a series of case studies following patient progress through the therapeutic regimen.

Ethnographic Methods

In-depth, unstructured and non-directive interviews[15] lasting from 60–90 mins were conducted with each patient in their home environments. The interviews were aimed at elucidating patient narratives,[16,17] medical history, prior experience with phantom limb pain and treatment therapies, and the broader holistic context of the person's life, family, hobbies, motivations, and personality. Yet acknowledging that people do not always readily articulate their behaviors and practices when asked about them, these interviews were complemented by participant observation[18] during rehabilitation. Employing a patient-centred approach to ethnography,[19] which emphasizes intimate attention to an individual's subjective and emic "experience-near," the anthropologist followed subjects in their homes, chronicling their strategies for navigating everyday life with their devices. These engagements reach beyond what subjects say in self-report into the realm of embodied practice.

Survey of Use Preference

A self-report questionnaire was administered to identify how long the subjects used each training exercise as well as whether they preferred a certain type over the other. In addition, the subjects were asked in an open-ended question for feedback about possible improvements of the system for home use. The results from the self-report survey were incorporated with the ethnographic data using the KJ Method to

develop insight into the themes and relationships among the qualitative data[20]. The basic steps of the KJ Method are as follows. First, quotes are extracted from a qualitative data source, such as interviews or surveys, and written down on separate cards. The quotes are then scanned to identify common themes, and subsequently grouped together under the headings of these themes. These classifications are inherently subjective and decided upon by the researcher(s)' interpretation of the data. Further naming and subclassification of the assorted groups is then performed as needed. This classified data from the KJ Method was used to identify user types and suggest future requirements from the therapy regime.

Results

Usage data for the four participants were gathered over one year of study and are summarized in bar graphs showing adherence to the treatment, and in histograms showing the distribution of session durations. Self-reported pain levels over time are illustrated as trends of Pain Rating Index (PRI) over time. All the data are summarized per subject and illustrated in Figure 1–4 (one figure per subject), which consists of three panels (A–C). The results of the survey about use preferences are reported in Table 1.

Panel (A) of Figure 1–4 reports the trend of the self-reported level of pain as estimated by the PRI (range 0–45), presented as monthly average. The typical pain descriptors chosen by each subject are reported in the respective captions: as it can be noted from all figures, the level of pain remained relatively constant and low over time. Consequently, the pain descriptors also held stable, showing mild variations only within the individual ratings.

Each of the adherence bar plots (panel (B) in Figure 1–4) condense information about therapy adherence as percentage of the suggested monthly sessions carried out by each participant. Biweekly training (eight sessions per month) was considered the optimal treatment frequency. For example, the first bar of Figure 1B shows a treatment adherence of 137.5%, meaning that Subject 1 carried out 11 training sessions during the first month. Note that the subjects started the home treatment in different months; it ensues that "month 1" in the x-axis does not correspond to a specific month but rather the start of the treatment for that specific subject. The number on top of each bar represents the average number of movements per recording session month by month. The training software theoretically allows the user to train up to 18 movements simultaneously. However, patients can rarely achieve above six movements due partly to the limitations posed by MPR with surface EMG and a limited number of recording channels (up to eight, in the device used). Reporting the monthly average of movements performed per recording session is taken to

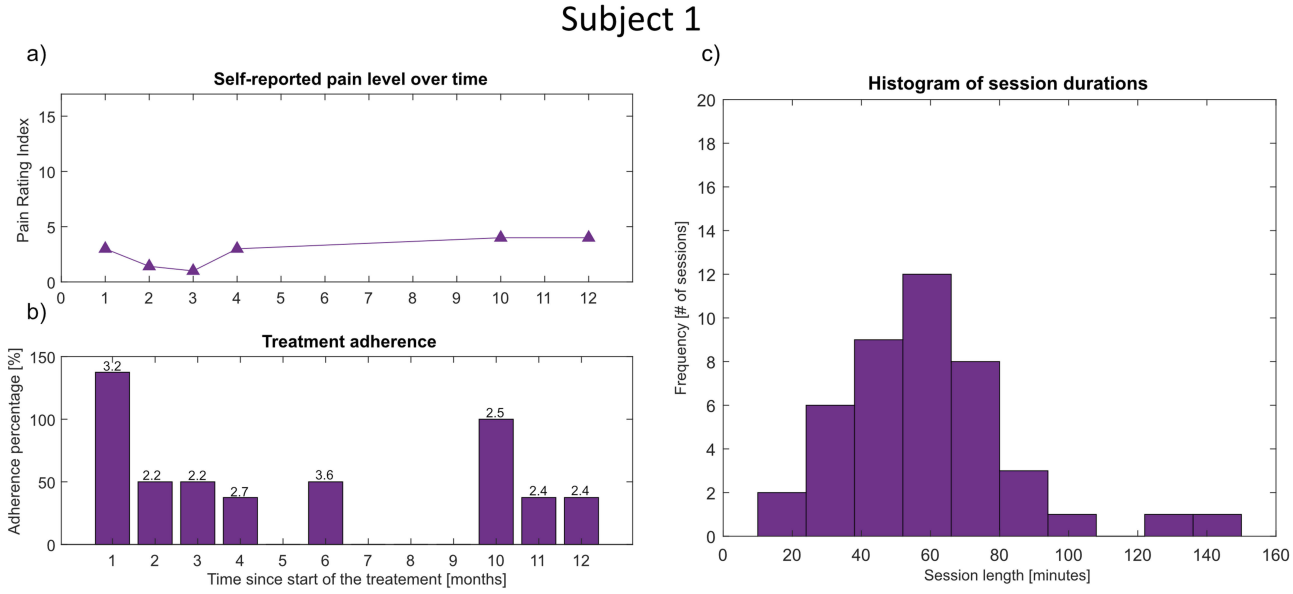

Figure 1 Panel (**A**) presents the self-reported level of pain as expressed by the Pain Rating Index (the sum of the scores give to the chosen McGill pain descriptors) over time (x-axis). The range of the PRI is between 0 and 45 however the range of y-axis of this graph has been reduced to 0–15 to improve the quality of the data visualization, since this is the interval containing the PRI for all participants. The value presented in the graph is the monthly average (y-axis). Pain level was not reported in those months where no data points are shown. (**B**) Treatment adherence data expressed as percentage of the suggested treatment frequency (eight sessions a month). The number presented on top of each bar represents the average number of movements trained in a given month. (**C**) Histogram of the session duration, each bar represents the number of session (value on the y-axis) of a given length (value on the x-axis). Figure 1 presents data relative to Subject 1. The only pain descriptor reported by Subject 1 is hot-burning.

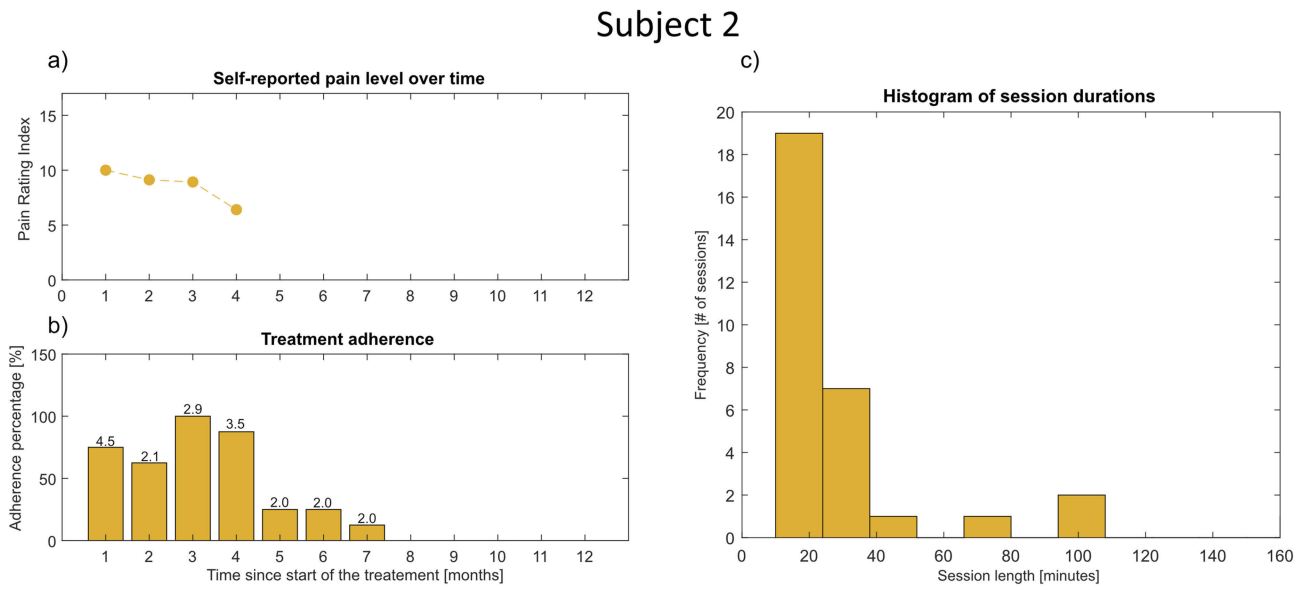

Figure 2 Data relative to Subject 2 presented in an analogous way to Figure 1. Panel (**A**) presents the self-reported level of pain; (**B**) treatment adherence; (**C**) histogram of the session duration. Typical pain descriptors reported by Subject 2 were: throbbing, shooting, stabbing and aching.

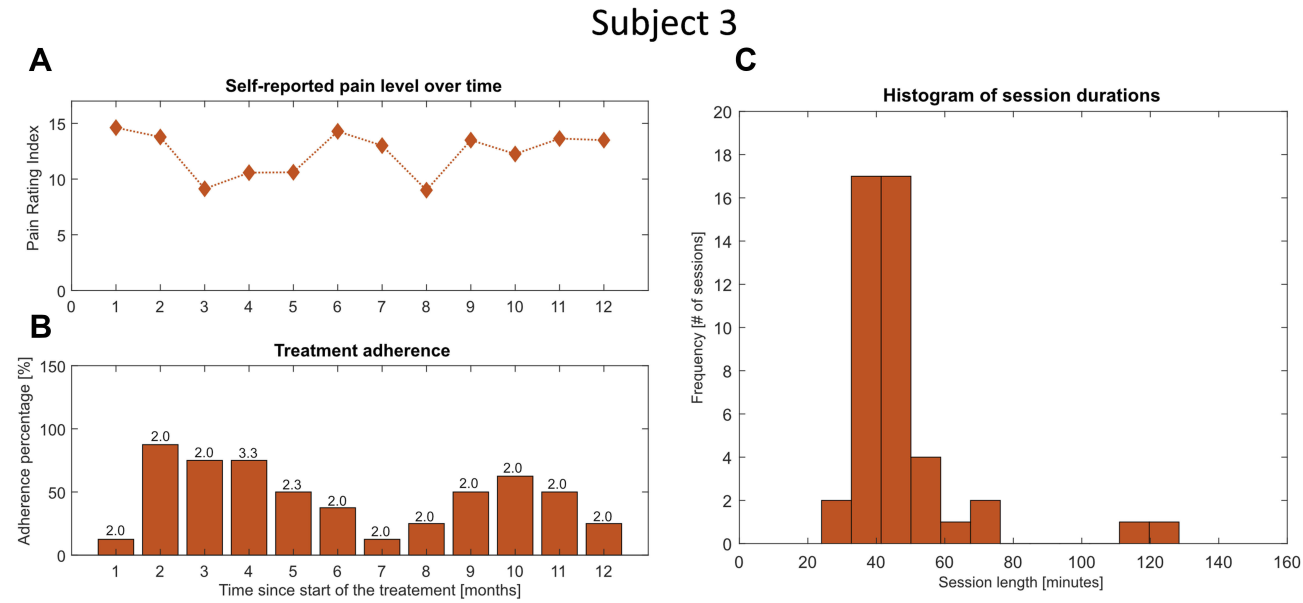

Figure 3 Data relative to Subject 3 presented in an analogous way to Figure 1. Panel (**A**) presents the self-reported level of pain; (**B**) treatment adherence; (**C**) histogram of the session duration. Typical pain descriptors reported by Subject 3 were: throbbing, stabbing, sharp, gnawing, hot-burning, aching and splitting.

indicate the complexity of the exercises carried out: the more movements trained within the same recording session, the higher the complexity of the classification task for the MPR algorithm. An increasing number of movements requires superior motor skills of the stump musculature in order to maintain quality performance with the VR/AR and SG environments.

From this way of presenting adherence data, it becomes clear that over the course of the first seven months the usage frequency generally decreases among all subjects. Subject 1 starts in January and interrupts the treatment between July and September, resuming the therapy with 100% adherence in October. S2 starts in August but phases out completely by March. S3 starts in December and trains throughout the

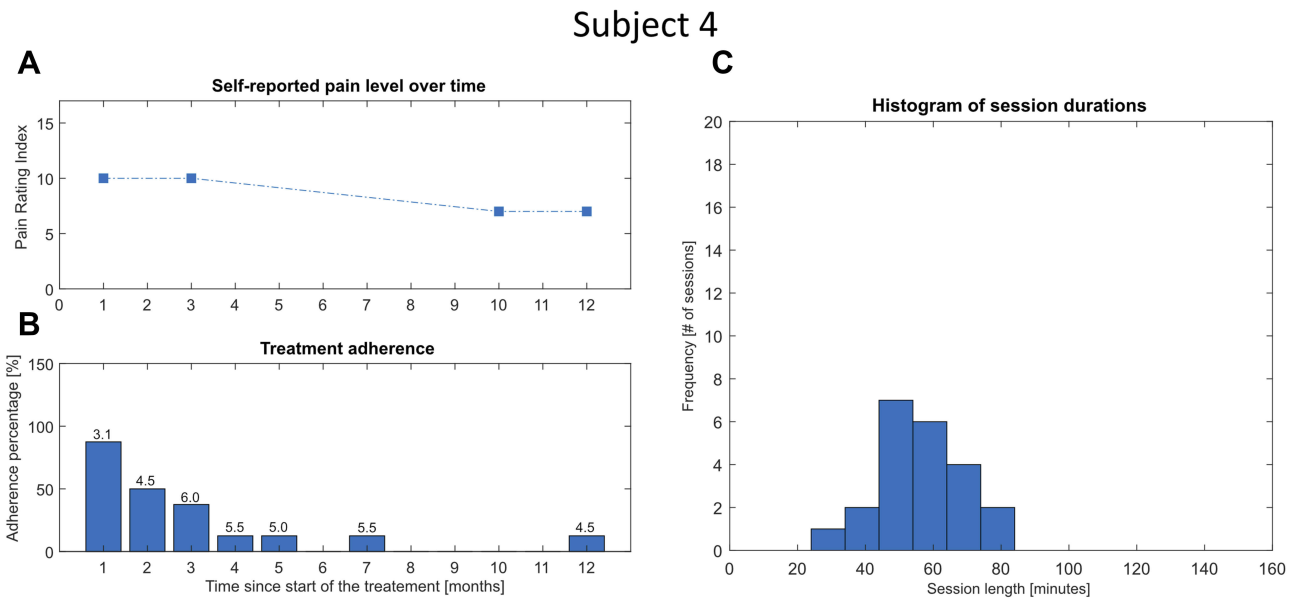

Figure 4 Data relative to Subject 4 presented in an analogous way to Figure 1. Panel (**A**) presents the self-reported level of pain; (**B**) treatment adherence; (**C**) histogram of the session duration. Typical pain descriptors reported by Subject 4 were: cramping, gnawing, heavy, tender, tiring-exhausting, punishing-cruel.

whole year: the frequency of training decreases in over summer months only to increase again during the following winter. S4 starts in October and trains with decreasing frequency over the following 7 months; after a long interruption of four months, she returns to therapy at the end of the monitoring year.

The complexity of the movements appears idiosyncratic; for each subject such idiosyncracy remains relatively constant over time. Session duration, in panel C, is presented in the form of histograms and indicates that all subjects spent less time training than the advised 90 mins, but also shows a large within-subject variation of session length.

Table 1 Self-Reported Use Preferences Using PME Device

Self-Reported Use Preferences	S1	S3	S4
Therapy Duration	1.5 hrs-2 hrs	1 hr-1.5 hrs	1.5 hrs-2 hrs
Average TAC Time	0–10 mins	More than 20 mins	15–20 mins
Average AR Time	More than 20 mins	More than 20 mins	0–10 mins
Average VR Time	I do not use the VR Limb	More than 20 mins	0–10 mins
Average Game Time	0–10 mins	I do not use the race car game	I do not use the race car game
Preferred Exercise	AR Limb	TAC Test	TAC Test
Factors that Prevent you from doing therapy	Time Shortage	Number of Electrodes	Time Shortage
What additional assistance do you need to carry out the session	None	Not needed, practiced many times and learned by doing	Someone who feels where to place the electrodes on the muscles
Progress Marker	Increase in Sleep, decrease in daily pain levels	Pain decreases by 30–50%	-
Open Recommendations	-	Reusable Electrode interface, shorter treatment times more often	More exercises with a goal to reach, and reduce timing

Abbreviations: PLP, phantom limb pain; MPR, myoelectric pattern recognition; PME, phantom motor execution; AR/VR, Augmented and Virtual Reality; SG, serious gaming; TAC, Target Achievement Control; SF-MPQ, Short Form of the McGill Pain Questionnaire; PRI, pain rating index; PMI, Phantom Motor Imagery.

Table 1 displays the results of the user preference survey. It was not possible to survey S2 because he terminated the use of the device several months preceding the interview time. From these results a discrepancy emerges in the estimate of time spent training as inferred from the data stored in the software (panel C of Figure 1–4) versus the data reported by the users themselves (Table 1), with the latter always exceeding the former.

Ethnographic Results

Ethnographic results are first presented for each subject, followed by ethnographic analysis of cross-cutting themes among all subjects, elucidating four key findings. All descriptors regarding the therapy and pain experiences that are contained in quotations are subjects' own words from interviews with the anthropologist. These descriptors were chosen by the subjects themselves, elicited through their own free-associations, rather than offered as prompts in the interview. Descriptors regarding therapy and pain experience that are not contained in quotations are the anthropologists' observations and interpretations drawn from participant observation as well as themes present in the interviews.

S1 reported a shift in frequency and consistency of his at-home treatment, largely depending on his level of present pain and corresponding motivation. For the first few years using PME at-home, S1 practiced the therapy regularly:

> It was much simpler for me to use the system at home. I started with ambition. If I did it every day, what would happen? For a time I used it every other day, just to see if the pain were to disappear even more, but there actually wasn't too much of a difference.

After a few months of frequent sessions at home, S1 was able to stabilize his pain levels with less regular intervals of the therapy. When pain was manageable, S1 deprioritized the therapy. "I wish I did it a bit more often," S1 admitted. "I'm not hindering you!" S1's wife chimed in. S1 acknowledged that his wife often reminds him to practice the therapy, citing that she can "sense a difference" when he has been more regular with the treatment. Still, "life gets in the way," as he explained, and sometimes weeks pass between his treatment sessions:

> It's easy to say 'no, I have to do this first.' So that is the problem when one is responsible at home for their own treatment. One must prioritize the treatment. When I start to feel that the pain is becoming a problem again, then I prioritize it. When the pain isn't so bad, I think 'not just now, I can do it tomorrow.

Here, S1 highlighted the challenge of in-home treatment maintenance when pain is not so present or acute and that the use of the therapy is often driven by current pain level. S1 reported that he typically performs a treatment session for two hours. Despite years of using the AR/VR device, S1 continued to find enjoyment and novelty in the treatment. "It doesn't feel like (two hours) because it takes so much concentration, it's so fun even after all these years … it's not very easy, it requires concentration, it isn't the same every time," he reflected. S1 progressed through all four activities but tends to prefer the AR configuration and the TAC test. A former professional race car driver, S1 enjoyed playing the game, especially delighting when he can steer the car with movements from his little finger, motivated by reaching a "best time." Despite his familiarity with the device, some elements, including electrode placement on the skin of the residual limb to record clear myoelectric signals, remained "challenging" throughout the course of the study. From time to time signal quality still varies. One time I got such good signals that I took a permanent pen and marked on my skin where they were. But it washed away after a few showers. This one is easy, he points to one electrode that lay just above a scar, "I just follow the scar slightly up." As S1's description demonstrates, in-home use of the AR/VR device requires learning and knowing the locations on one's body in relation to signal quality. During one treatment session, the anthropologist noticed S1 whispering under his breath, intently focused on the virtual on-screen hand, coaxing the little finger as if he were addressing a young child. This moment evinced the degree to which patients like S1 envision the virtual arm as intimately connected to the user's own body – if not a virtual representation of one's own phantom hand, then at least something which they can guide and control with effort and positive self-talk. "The best part is when I can control these little fingers here," he points to the fourth and fifth fingers. "That happens just a few days a year. It happened just three nights ago!" This challenge—seeing if he can control the two little fingers—seemed to drive each and every treatment session, his barometer of success. "The brain realizes that one can move the little fingers; it realizes they (still) exist there," he explained. His invocation of the brain speaks, uncannily, to the underlying theory of PME.

S2 is a unique patient in that he adapted PME therapy to not require the use of the AR/VR device, a regimen he

calls "in-head exercises." S2 ceased the use of the device because he felt only a few minutes of training was necessary to achieve pain relief, and this was not worth the time required to place the electrodes. When the research team visited S2 at his home, they were most interested in better understanding how he practices PME without the AR/VR device. It was crucial to ensure S2 was not merely envisioning or imagining the movements in his mind (which would purportedly only engage Phantom Motor Imagery [PMI]) but rather that he was actively engaging the muscle groups around the stump to execute movement in the phantom arm and hand (purportedly engaging the sensorimotor system). S2 described his method as such: He sits or lays on the sofa and tries to relax, directing his attention to the phantom pain (which he otherwise tries to avoid it through distraction). He first thinks about the movement, then performs the movement, feeling the muscles in his residual limb contract. In this description, S2 made a clear distinction between passively thinking and actively performing the movement, signaling to the research team that he was in fact engaging the muscles in the way PME intends. Like the other three subjects, S2 developed his own routine for practicing PME, yet his was more frequent with a much shorter duration: he trained roughly four times a day, for just one to two minutes at a time. The exercise he most often performed was opening and closing his phantom hand. It took only one minute before he started to feel the pain diminish. Still, S2 continued to take oxycodone to manage his pain every day. However, he has greatly decreased his intake of pain medications, halting his earlier use of morphine plasters and using low-dose tablets instead. Still, it appeared that PME exercises served as a supplement, while morphine remained his first-line treatment. Interestingly, even though they did not currently have an AR/VR device at home, S2 and his wife took meticulous care of its operating instructions, which they kept in a binder with pages laminated. In this binder, they had pictures of S2's stump with the electrodes placed in their optimal position for producing the clearest signals (his physiotherapist's idea). Even despite his current non-use of AR/VR device, S2 acknowledged its importance in initiating his own treatment practice. "Without the device, I would have never come up with this method," S2 said, referring to his "in-head exercises." S2's case testifies to the possible efficacy of PME independent of the therapeutic technology developed and traditionally used to facilitate it.

S3 was the subject who most enlists his family's help in the therapy's practice. His wife participated actively in each session, helping him set up the device, place the electrodes on his stump, and navigate the program's various activities on the laptop. His son was often involved as well, troubleshooting when the program has any technical difficulties, and was also the main point of contact between S3 and the researchers. S3 also created the most strictly regimented schedule for his PME treatments, built into his family's weekly routine: every Monday and Thursday, around 5 or 6pm, before dinner. Each training session, S3 began with a different leg movement. After completing the recording session, he skipped the Virtual Reality portion of the treatment, often preferring the Augmented Reality version. In fact, he spent a majority his time with AR/VR device using the Augmented Reality; he disliked the car racing game as he found it tedious and difficult to control ("I just kept crashing the car"). S3's son, who was actively involved in the treatment, encouraged his father to use the TAC test, reasoning that "it's better because there's something to follow . . . so you know what you're doing," but S3 seemed to prefer using the Augmented Reality for its videocam representation of himself, the room, and his virtual leg. The anthropologist visited S3 twice – first with the research team and then alone – and found that the patient responded positively to the research team's suggestions and advice with regards to adherence and motivation. On the first visit, the patient seemed to be struggling with the treatment and unabated pain. A researcher identified S3 failed to follow the treatment instructions. S3 had not been increasing the level of challenge by performing new movements. The researcher then stressed the importance of this progression for the efficacy of the therapy. On the follow-up visit, the anthropologist observed a marked behavioral, even emotional shift in the patient's interaction with the technology. S3's stamina and tolerance appeared much higher, he grew less frustrated with the system, and the overall sense of motivation, enjoyment, even "belief" (his own descriptor) in the therapy, seemed much higher by the end of the study. Concomitantly, the patient reported a "reduction" in his phantom pain in the weeks following the implementation of a refocused approach, as per the research team's advice. Of all in-home patients, it seemed that S3 and his family had folded the AR/VR device into their home environment in the most intimate way, with specific household arrangements that facilitated the technology's use. Unlike the other patients, who used their laptop screen for the

treatment, S3 broadcasted the AR/VR exercises from his laptop onto a large TV screen in the living room. His wife and he purchased the laptop specifically for using the PME software. They stored the laptop and device on a roller-cart, which they covered with a towel, the same towel that S3 later placed on top of a chair to sit on when he performs the treatment. S3 and his wife have appropriated other everyday home objects into helpful tools that enabled the use of the AR/VR device. Since the reference electrode placed on S3's wrist often slipped due to sweat, they regularly placed a rubber band around it. S3 and his wife pasted the AR-reference, a barcode-looking piece of paper used to track the virtual arm onto the webcam of the patient's body, onto the cover of an old hardcover book, which they placed at the foot of S3's chair when not in use. S3's wife also recorded S3's activity scores in a handwritten notebook, actively participating in her husband's treatment. This manual progress-tracking constituted a form of care and sociality formed around the therapy.

S4 began her in-home PME treatment on the suggestion of a friend who was familiar with the treatment. She began to notice that it was "working" (her term) when one night, two months after she started the treatment and for the first time in nine years, she forgot to take her oxycodone pill. To her surprise, she slept an entire night without pain. She then continued ceasing her pills for one month but kept practicing PME. Several weeks later, she also stopped her PME treatment, thinking "it had worked" and was no longer necessary. But one month later, the PLP and disrupted sleep returned. This initiated a period of titrating between oxycodone and PME. S4 took the pill on and off, and began training with AR/VR device again, just twice a month. Five months after initiating the in-home treatment, she had continued this titration process, moving between sporadic oxycodone use and sporadic PME training to regulate her pain. S4 found that when she is not taking oxycodone, she was "more awake, energetic, less groggy," and had more responsive reflexes. At the beginning of her treatment, S4's at-home PME sessions would last 1.5–2 hrs. After several treatments, she reduced their duration to 1–1.5 hrs. While at the outset she utilized all of the AR/VR device activities (VR, AR, TAC Test, and gaming), she preferred to use the TAC Test, finding it "most helpful and effective" and began focusing her time and energy solely on that activity. At the time of the interview, her PME regimen consisted of a recording session for multiple simultaneous movements and two to three rounds of the TAC Test, which takes her roughly 1 to 1.5 hrs. For S4, a decrease (or cessation) of oxycodone signified the efficacy of PME as a stand-in treatment. Her assessment of whether the treatment was "working" changed over the course of the study in proportion to her use of it (more consistent use correlated to greater perceived efficacy). Her approach to focusing on the TAC Test also evinced an optimization of the treatment to fit her needs, a personalization of the therapy. S4's affinity with the TAC Test spoke to her broader identity as a professional athlete, motivated by the pursuit of scoring points and reaching goals. As S4 explained, "The TAC Test is an exercise where you have to reach the goal." She described this goal-reaching aspect as motivating; a higher score yields greater satisfaction. After several months of using the AR/VR device, she expressed that she had identified how to reach a higher score: she must optimize the electrode placement positioning on her stump. S4's goal score for each treatment session was 100%; she repeated the test until she reached as close as possible and attempted to repeat this two or three times. As such, her treatment session was guided less by a specific set time length, or by the progression through the PME exercises, but by the achievement of her self-identified "goal" (100% on the TAC Test). S4 found the AR/VR device itself a bit cumbersome; the software was not compatible with her Mac laptop, so she had to borrow her grandmother's PC laptop. S4 learned to place the electrodes on her stump herself but enlisted the help of friends in their placement, as well as over Skype with the research team in Gothenburg.

The analysis of ethnographic research elucidated the following four key findings:

1. Subjects developed their own PME routines surrounding frequency of practice and which activities they prioritize (and deprioritize). These routines varied from several-minute micro-sessions practiced four times daily (S2), to regularly scheduled bi-weekly evening sessions (S3), to more sporadic ad-hoc use based on severity of pain and perceived "need" for the treatment (S1 and S4). Subjects worked the treatment into the contexts of their everyday lives and saw the value of being able to practice the therapy on their own time without having to travel to the clinic. At the same time, sometimes life "gets in the way" (S1) and postponing or skipping treatment sessions became easier when competing with the demands of everyday life.

When this disruption occured, returning or increasing pain signaled to those without a regular PME schedule the need to re-prioritize their treatment.

2. Subjects customized and personalized PME to fit their bodies, pain levels, personalities, interests, and lifestyles. In doing so, they cultivated ways to stay motivated and engaged in the therapy. Patients personalized by prioritizing the AR/VR device activities that best align with their needs. S1 performed all activities sequentially, emphasizing the AR configuration and gaming, gauging his performance by his ability to move the fourth and little fingers of his phantom hand independently. S2 performed PME independent of the AR/VR device, thus proving the potential viability of the therapy absent of the device and its activities. S3 focused almost exclusively on the AR configuration, which he enjoyed most for its real-world reflection of his home environment, but also performed the TAC Test on the encouragement of his son, who believed it was more goal-oriented and thus motivating. S4 prioritized the TAC Test for its feedback of a percentage-based score; the pursuit of 100% tapped into her athletic goal-oriented motivation.
3. For most subjects, PME fit within the wider context of a pain management regimen. For three out of the four subjects, it was a supplemental treatment used in the context of continued low-dose pain medications, abating the need for higher dosage. While S1 had completely ceased use of pain medication since using PME, S2 and S3 still took low-dose pain meds daily. For these subjects, PME was a supplemental treatment that allowed them to manage their pain on a lower dose. S4 vacillated between taking pain meds and using PME, but unlike S2 and S3, she alternated these treatments rather than using them concomitantly.
4. In-home, the device became "domesticated" materially, contextually, and socially. Subjects like S3 recruited and adapted everyday home objects (books, roller carts, rubber bands etc.) into supplemental objects in the use of the AR/VR device, folding in the device into the material context of the home. In this way, it can be said that the device took up residence in subjects' households. Family members (in the case of S1 and S3) participated in the treatment – actively, in the case of S3, whose wife navigated the software interface and placed the electrodes on her husband's limb, and passively, in the case of S1, whose wife reminded and encouraged him to practice the therapy regularly. Thus, it was not only the subject, but also family members who engaged with the device both directly and indirectly.

Identification of User Types

The information regarding the use of the system was extracted from the ethnographic unstructured interviews and analyzed using the KJ methodology: Figure 5 summarizes the resulting workflow.

Proceeding subject by subject, the anthropologist read aloud relevant sections of the unstructured interview referring to the use of the system. The user researcher wrote down quotes and paraphrased information on separate cards. After reviewing each subject interview, the user researcher then organized the cards according to the themes that emerged: Personalized Dosing, Assistance/Support System, Definition of Progress, Motivation, Faith in Therapy, Storage of Device, Patient Improvisation, Electrode Placement and Tracking Progress. After studying these nine themes, the user researcher and anthropologist searched for discrepancies in themes within the groups to create further subgroups. The categories with notable discrepancies in themes included subjects' approaches to personal dosing, their definition of progress, their faith in therapy and their motivations for performing the therapy. The data under these categories was then subdivided into the two user types: the goal-oriented user and the experiential user. For the remaining five categories, no subcategorization was needed.

These user types are archetypes, informed by but not directly reflecting any one individual patient, used solely to contextualize the functional requirements for the design of the user interface. In some cases, patients straddled the two user types. The survey results support these two user types and also demonstrate differences in the time patients spend on each AR/VR activity.

User Type I: Goal Oriented User

These users mark their progress with PME based on completion of a goal, rather than cumulative time passed, and prefer goal-oriented activities such as the TAC test over time-based activities like AR or VR. These users could be more interested in feedback from the therapy in terms of markers for completion of certain goals. S3 and S4 both

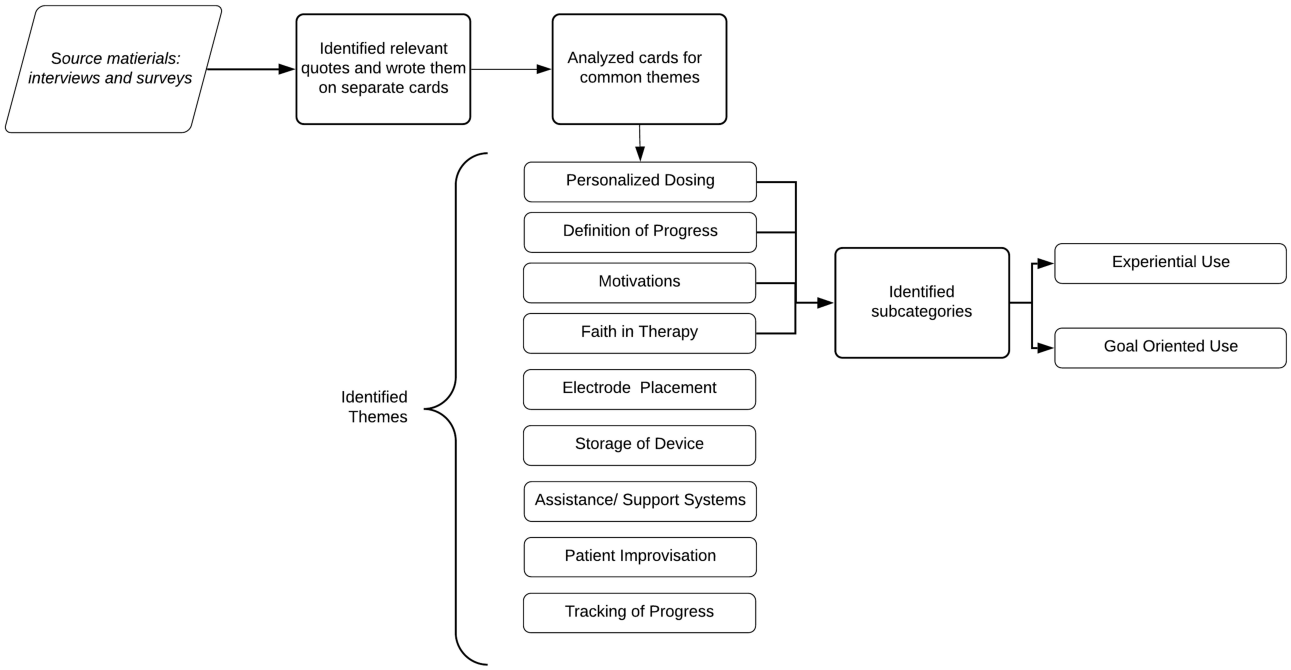

Figure 5 Flowchart presenting the steps and the results of the KJ analysis.

exhibit patterns of a goal-oriented user in that they both exhibit a preference to the TAC Test (see Table 1), in which the user strives to achieve a goal movement. While S3 identifies the TAC test as a preference, he also practices often with the AR limb, which also corresponds to User Type II patterns, indicating that user preferences are not always clear-cut between the two types.

User Type II: Experiential User

These users see the therapy regime through the scope of the AR experience, which renders the user's physical body and the virtual limb in the same screen using a webcam, also reflecting their actual environment. The Experiential User may place more importance on the realistic qualities of the AR limb in terms of sizing, colour and shape as well as how responsive and realistic the virtual limb is with regards to the user's perception of their phantom limb. This user will often base their practice more on a time marker than achieving a specific movement goal. This pattern of use was ascertained in observation of S3's preference for experiential practice through motor execution and S1s self- preference (see Table 1). It must be noted that patients may enter PME with previous experience from other forms of pain management therapies, including mirror therapy,[21–23] where visual feedback is considered the main conducive of pain relief: In these cases, the verisimilitude of the anthropomorphic feedback is of paramount importance. This introduces a potential discrepancy between the goal of PME therapy, which is based on the improvement of the motor execution, and the user's expectations and goals. This may translate into a preference for the anthropomorphic components of the PME therapy, such as the AR, disfavoring those components that do not involve a virtual limb, i.e. the racing game. Furthermore, mirror therapy sessions may be based off of practicing for a set amount of time rather than reaching a motor execution goal. In order to address this potential user bias and translate it into the new underlying theory of PME, a time-aware software interface should be developed in order to deliver feedback on the time spent at each level of movement difficulty (single degree of freedom movements, multiple degree of freedom movements, simultaneous movements) and motivate the patient to attempt more complex movements or to test their skills after the experiential practice.

Discussion

This study demonstrates the adaptability of a technological therapy (PME) to treat PLP in the home, where patients drive its usage. Hypotheses on the working mechanism of PME as a treatment of PLP, as well as for the genesis of the condition itself, have been discussed at length by Ortiz-Catalan along with clinical results and potential confounding factors.[1] The purpose of this study was not to

assess therapeutic efficacy but rather to interpret how a previously clinical therapy can be translated into home contexts, at the user's discretion. Subjects were instructed to use the AR/VR device at will, adapting it to their needs. The adherence data indicates that patients use the system more intensively in the first weeks of receiving the device, and then diminish their usage as pain decreases, as evidenced by lapses in use. Use is taken up again in an ad-hoc fashion, at need, often driven by the recurrence of pain. As a consequence, the pain graph might not necessarily depict how the treatment affects patients' pain, but rather how their pain level drives the use of the therapy. Treatment adherence, then, changes depending on patients' needs.

This tight coupling and interplay between pain, perceived need, and use requires a multidisciplinary approach. Alone, the pain rating does not reflect everything about the intricacies and motivations driving (or deterring) a patient's in-home device use. Therefore, we involved an anthropologist and user interface designer, along with their qualitative methodologies, to better understand use behaviors, patterns, and barriers. Their analysis indicates that users' profiles differ depending not only upon their needs, but also upon their motivations and daily life contexts. Patient adherence is especially important in this form of therapy because of the underlying mechanisms of PME.[1] This makes understanding and designing for different user groups and understanding user expectations a critical task to improving the adherence and outcome of the therapy regime at home.

The self-reported use preferences indicate two key barriers to adherence. The first is time. The therapy demands significant time (one to two hours per session), requiring the patient to incorporate the regimen into their everyday life. The second barrier is the need for reusable electrodes. The cost and availability of single-use electrodes can make the therapy prohibitively expensive or inaccessible and therefore could decrease adherence to therapy regime.

In order to design a device compatible with multiple user types, the following functions are recommended. For the Experiential User, a time display recording both duration and frequency will allow for tracking and recording within the interface. AR should be further developed to meet variations in skin color, nail color and size of limb, to expand relevance to wider, more diverse user populations and enhance their engagement. For the Goal Oriented User, feedback on results (i.e. movement accuracy measured by the TAC test, level of complexity of limb movement combinations) should be displayed to drive motivation. Additional goal-oriented activities and markers could recognize accuracy on different combination of movements. Indeed, the average number of limb movements shown in panel B of Figure 1–4 does not evidence any significant increase over time, indicating a need for the software to prompt the patients to increase difficulty.

Users should be enabled to set personal goals for the therapy using different measures of success (i.e. Increase Movement Accuracy, Decrease Pain, Improve Sleep Quality). User data (adherence, TAC scores, time) should be comprehensively presented as a form of feedback and self-monitoring. This underscores the need for ways to track long-term progress, considering breaks in therapy and consequent need to refresh PME skills. Finally, feedback on progression and level of complexity of movements needed in therapy will make treatment sessions more efficient.

The main limitations of this study include a small sample size (n=4). The inherent variability of patients' home situations makes generalizability difficult, but also serves to demonstrate the versatility and flexibility of both the device and its therapeutic applications. Patients have adapted the regimen to their home lives and developed personalized routines. This paper is a proof of concept. Future research should focus on a more systematic and robust investigation on the home use of the device, including compliance over a longer period of time.

Conclusion

This study holds methodological relevance for a broader research context beyond that of phantom limb pain. Healthcare services and therapeutic technologies are increasingly moving outside of the clinic into the home, a global trend growing with the digitization and development of artificial intelligence and user-friendly design. This domestication of health technology raises both new possibilities and challenges, as well as creates unprecedented encounters between humans and technologies in their own domain, demanding a new approach to studying these relations. This paper offers an example of how to study and monitor the use of such health technologies in the home. By including the social expertise of a medical anthropologist and the human-machine interface expertise of a user interface designer, we approach this phenomenon holistically adding a social perspective to a question that would normally be answered in terms of clinical and quantitative data. What emerges is a more nuanced picture of the motivations, barriers, and desires driving patient-led

in-home care, which in turns is used to design interventions that increase the technology's capacity and relevance.

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