THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Surgical Advancements for Individuals with Limb Amputation

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Cover: The illustration visualizes innovative surgical approaches in amputation care, featuring Targeted Muscle Reinnervation, Osseointegration, and Regenerative Peripheral Nerve Interface for improved function and pain relief.

Cover illustration created by the author, Emily Pettersen.

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“In the middle of difficulty lies opportunity.”

— Albert Einstein

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Abstract

Individuals facing major limb amputation confront two primary challenges: restoring lost function and managing amputation-related pain. In recent decades, surgical and engineering innovations have significantly advanced rehabilitation in both areas. However, their full potential has yet to be realized in terms of optimization and widespread adoption, underscoring the need for continued research.

One breakthrough in functional restoration is the development of bone-anchored "osseointegrated" limb prostheses, which involve directly attaching a prosthesis to the skeleton. This approach enhances functionality by addressing the limitations of traditional socket prostheses, such as skin irritation and nerve compression. However, achieving a successful bone-implant interface is critical for long-term efficacy, and in some cases, the osseointegration process must be enhanced. In pain management, surgical advancements such as selective nerve transfers and muscle reconstruction have become increasingly common, driven by techniques designed to promote healthy nerve regeneration after neuroma removal. The two most widely used methods, Targeted Muscle Reinnervation (TMR) and Regenerative Peripheral Nerve Interface (RPNI), have shown promising results in treating and preventing postamputation pain. Despite encouraging results, rigorous comparative studies against the current standard of care are lacking, and clear guidelines for standardized application of these procedures remain undeveloped.

This doctoral thesis explores a potential advancement in osseointegration while also contributing to the dissemination and implementation of existing surgical techniques. To address the functional challenge, we introduced a novel concept that uses pulsed electrical stimulation, mimicking peripheral nerve stimulation in artificial limbs, to enhance osseointegration. This concept leverages existing hardware and well-established stimulation paradigms within known safety parameters. This approach shows promise in accelerating healing, restoring early function, and reestablishing osseointegration in failing bone-anchored implants.

To address the knowledge gap in pain treatments, we designed a multicenter, international randomized controlled trial (RCT) comparing TMR and RPNI to each other and to a standard procedure, in order to evaluate their effectiveness in treating postamputation pain. This represents the first and largest RCT directly comparing these techniques. As part of the study, we convened leading global experts in the field to standardize the surgical procedures, resulting in comprehensive written protocols and video recordings. Each step was thoroughly discussed and defined by the experts to ensure clarity and consistency. This work also contributes to the dissemination of these techniques, facilitating their implementation and providing a valuable resource for clinicians seeking to integrate them into amputation care practices.

Keywords: Amputation, Osseointegration, Postamputation Pain, Residual Limb Pain, Phantom Limb Pain, Targeted Muscle Reinnervation, Regenerative Peripheral Nerve Interface, Randomized Controlled Trial

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Emily Pettersen, Gothenburg, October 2025

List of Publications

This thesis is based on the work contained in the following articles:

Paper I

"Electrical stimulation to promote osseointegration of bone anchoring implants: a topical review", **Pettersen E**, Anderson J, Ortiz-Catalan M. *Journal of NeuroEngineering and Rehabilitation*. 2022 Mar 21; 19(1):31.

Paper II

"Enhancing osteoblast survival through pulsed electrical stimulation and implications for osseointegration", **Pettersen E**, Shah FA, Ortiz-Catalan M. *Scientific Reports*. 2021 Nov 17; 11(1):22416.

Paper III

"Surgical treatments for postamputation pain: study protocol for an international, double-blind, randomised controlled trial", **Pettersen E**, Sassu P, Reinholdt C, Dahm P, Rolfson O, Björkman A, Innocenti M, Pedrini FA, Breyer JM, Roche A, Hart A, Harrington L, Ladak A, Power H, Hebert J, Ortiz-Catalan M. *Trials*. 2023 May. Erratum in: *Trials*. 2023 Oct 9; 24(1):654.

Paper IV

"Targeted Muscle Reinnervation: Surgical protocol for a randomized controlled trial in postamputation pain", **Pettersen E**, Sassu P, Pedrini FA, Granberg H, Reinholdt C, Breyer JM, Roche A, Hart A, Ladak A, Power HA, Leung M, Lo M, Valerio I, Eberlin KR, Kung TA, Cederna P, Souza JM, Aszmann O, Ko J, Dumanian GA, Ortiz-Catalan M. *Journal of Visualized Experiments*. 2024 Mar 8;(205).

Paper V

"Regenerative Peripheral Nerve Interface: Surgical protocol for a randomized controlled trial in postamputation pain", **Pettersen E**, Sassu P, Pedrini FA, Granberg H, Reinholdt C, Breyer JM, Roche A, Hart A, Ladak A, Power HA, Leung M, Lo M, Valerio I, Eberlin KR, Ko J, Dumanian GA, Kung TA, Cederna P, Ortiz-Catalan M. *Journal of Visualized Experiments,* 2024 Mar 15;(205)

Acronyms

AMI	Agonist-antagonist Myoneural Interface
C-RPNI	Composite Regenerative Peripheral Nerve Interface
CMI	Cutaneous Mechanoneural Interface
DC	Direct Current
DoF	Degree of Freedom
EBM	Evidence-Based Medicine
EMG	Electromyography
IASP	International Association for the Study of Pain
ITT	Intention-To-Treat
MC-RPNI	Muscle Cuff Regenerative Peripheral Nerve Interface
NRS	Numerical Rating Scale
OPRA	Osseointegrated Prostheses for the Rehabilitation of Amputees
PLP	Phantom Limb Pain
PLS	Phantom Limb Sensations
PP	Per-Protocol
RCT	Randomized Controlled Trial
RLP	Residual Limb Pain
ROS	Reactive Oxygen Species
RPNI	Regenerative Peripheral Nerve Interface
TMR	Targeted Muscle Reinnervation
TRL	Technology Readiness Level
TSR	Targeted Sensory Reinnervation
VDMT	Vascularized Denervated Muscle Target

Contents

Part I

Introductory Chapters

CHAPTER 1

Introduction

Major limb amputation is a life-changing event with profound and lasting effects on an individual's overall quality of life[1]. Those affected often encounter numerous challenges, including reduced independence, difficulty performing daily activities, struggles in maintaining social relationships, and an inability to return to work[1, 2]. Additionally, individuals with limb loss frequently experience pain in the residual limb or the missing body part, which further impacts their physical and emotional well-being[3–5]. Beyond these personal challenges, societal biases against disabilities can lead to social stigma, discrimination, and barriers to accessibility, all of which compound the difficulties faced by individuals with amputations[6].

Effectively addressing limb loss requires a comprehensive approach aimed at both restoring lost function and managing amputation-related pain (*Figure 1*). Advances in prosthetic technology, medical innovations, and rehabilitation strategies have led to significant improvements, offering people with limb loss more effective replacements[7–9]. However, despite these advancements, currently available prosthetic solutions remain vastly inferior to biological limbs in terms of functionality and somatosensory feedback. Furthermore, pain after amputation, including pain in the residual limb and the missing body part, remains a prevalent and complex challenge that is often difficult to treat effectively[10].

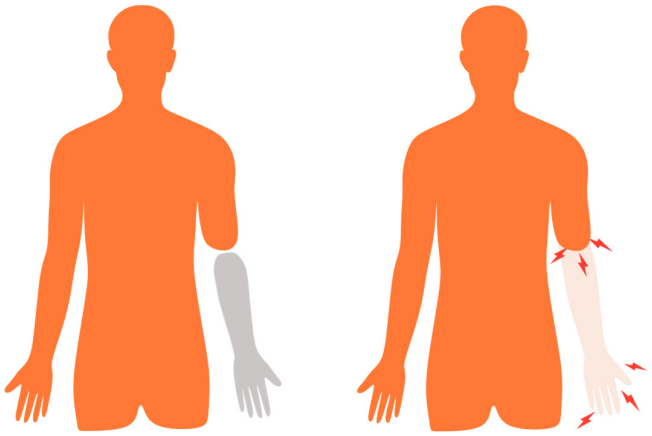

Figure 1. *The main needs of individuals after major limb loss include restoring lost sensorimotor function and managing amputation-related pain.*

Currently, millions of people worldwide are living with upper or lower limb amputations[11]. In the United States, an estimated 1.6 million individuals had undergone limb amputation by 2005, with this number projected to rise to 3.6 million by 2050[11]. Lower limb amputations are more prevalent, accounting for 65% of all amputations. Among these, 39% are classified as major amputations and 26% as minor. Upper limb amputations constitute the remaining 35%, with minor amputations (32%) being significantly more common than major amputations (3%)[11]. The prevalence of major lower limb amputations is estimated at 17 to 25.8 per 100,000 individuals in studies conducted in Sweden and the USA, respectively[11, 12]. In contrast, major upper limb amputations range from 11.6 to 13.9 per 100,000 individuals in studies performed in Norway and the USA, respectively[11, 13].

The most common causes of amputation vary depending on the affected limb. In upper limb amputations, trauma is by far the leading cause, followed by vascular conditions and cancer[14]. In contrast, lower limb amputations are most commonly caused by vascular insufficiency, followed by diabetes, trauma, and cancer[15]. Generally, individuals undergoing major upper limb amputation tend to be younger and healthier, whereas lower limb amputations more often affect older individuals with significant comorbidities[12, 14]. Major traumatic amputations are significantly more common in males, typically resulting from motor vehicle accidents or machinery-related injuries[16].

Advancements in surgical techniques over recent decades have significantly contributed to restoring function and managing postamputation pain. Notable innovations include bone-anchored osseointegrated implants, which allow for direct skeletal attachment of prosthetic limbs[17–19], and selective nerve transfers combined with muscle reconstruction, which improve prosthetic control[20–30] and reduce the risk of painful neuroma formation following nerve transection[31, 32]. Despite these advances, clinical adoption of such techniques remains limited. For instance, bone-anchored prostheses present several inherent challenges, including the need for surgery, strict daily hygiene routines, and limitations in high-impact activities, as well as clinical risks such as implant fractures and infections. These factors must be carefully considered to further optimize the technique and expand its use.

As another example, in the updated amputation protocol from November 2024 at Sahlgrenska University Hospital, the largest hospital in Northern Europe, it is recommended that nerves be "*transected under traction and positioned in a way that prevents a neuroma from causing problems with prosthetic fitting.*"[33] This method has increasingly been regarded as outdated by researchers and specialists over the past decade[34–36], yet it continues to be endorsed in protocols at leading institutions.

1.1 Thesis Scope

Surgical advancements in amputation rehabilitation have proven highly effective in addressing both functional restoration and pain-related challenges. However, their full potential remains unrealized due to the need for standardization, further optimization, and broader clinical adoption. This doctoral thesis investigates a novel approach to enhance osseointegration while also contributing to the standardization and dissemination of established surgical techniques for pain treatment. In detail, this research focuses on:

- Exploring the approach of using electrical stimulation as a modality to promote osseointegration.
    - Literature review (*Paper I*[37]).

- Investigating the concept of using pulsed electrical stimulation, with characteristics resembling those used for peripheral nerve stimulation, to promote osseointegration.
    - Design and performance of an *in vitro* study (*Paper II*[38]).

- Designing a randomized controlled trial (RCT) to provide high-quality evidence for the efficacy of surgical reconstructive techniques in treating postamputation pain.
    - RCT protocol (*Paper III*[39]).

- Standardizing surgical techniques to minimize bias within the RCT and facilitate dissemination of the procedures.
    - Surgical step-by-step protocol for Targeted Muscle Reinnervation (*Paper IV*[40]).
    - Surgical step-by-step protocol for Regenerative Peripheral Nerve Interface (*Paper V*[41]).

1.2 Thesis Outline

This thesis is divided into two parts. Part I introduces the field and offers essential background knowledge for understanding the included scientific articles. This introduction is followed by Chapter 2, which summarizes conventional clinical solutions for artificial limb replacement and highlights their limitations. Chapter 3 presents advanced clinical solutions, such as osseointegration and selective nerve and muscle transfers, that address some of the limitations discussed in the previous chapter.

In Chapter 4, the use of electrical stimulation as a modality to promote osseointegration is introduced, and a novel stimulation concept is proposed to enhance this process. Chapter 5 shifts focus to the second major challenge following amputation: postamputation pain. Chapter 6 presents surgical treatments for postamputation pain, summarizing both non-reconstructive and reconstructive procedures, and highlighting their limitations. This chapter also discusses barriers to the implementation of reconstructive procedures and identifies current knowledge gaps in the field.

Chapter 7 outlines the design of an RCT, while Chapter 8 describes the standardization protocols for the surgical techniques Targeted Muscle Reinnervation (TMR) and Regenerative Peripheral Nerve Interface (RPNI). Chapter 9 summarizes the thesis contributions, and Chapter 10 offers concluding remarks and suggestions for future work.

Part II of the thesis includes five peer-reviewed scientific articles developed during this doctoral project.

CHAPTER 2

Conventional Clinical Solutions for Artificial Limb Replacement

The main clinically available solutions for individuals with limb amputations have remained largely unchanged over the past decades. Although research continues to advance, replicating the full functionality of a biological limb remains a significant challenge, and many innovations have yet to transition from the laboratory to everyday use.

2.1 Challenges of Artificial Limb Replacement

Replacing a biological limb with an artificial one to restore lost function presents significant challenges. These challenges can be broadly categorized into four areas: the prosthetic device itself, attachment to the user, control mechanisms, and provision of somatosensory feedback (*Figure 2*). Additionally, the level of amputation influences the specific requirements and complexity within each category. Certain challenges become more relevant depending on the level of limb loss. For instance, in upper limb amputations, the primary goal is to restore fine motor function lost with the hand, whereas in lower limb amputations, the emphasis is on achieving a stable and natural gait.

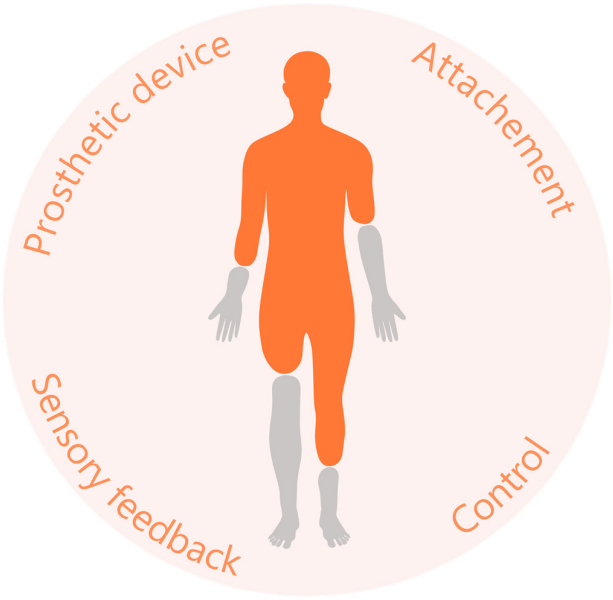

Figure 2. *The four main challenges of artificial limb replacement include the prosthetic device, mechanical attachment to the user, control of the prosthesis, and provision of sensory feedback.*

Prosthetic Devices

Nowadays, upper limb prosthetic options range from purely cosmetic designs that resemble the natural appearance and offer basic stabilization without functional capabilities, to traditional body-powered devices. These body-powered prostheses are generally more affordable, require less maintenance, and are known for their mechanical robustness, although they offer limited dexterity and range of motion[42]. A more advanced alternative is the myoelectric prosthesis, which exploits muscular activity in the residual limb or surrounding muscles via surface or implanted sensors. These

signals are translated into electrical commands that control motorized joints, enabling more natural and stronger movements, such as improved grasp strength, compared to body-powered systems[43]. Lower limb prostheses, meanwhile, span from passive weight-bearing supports that aid in balance and standing to active or semi-active devices equipped with microprocessors, sensors, and actuators that enhance dynamic functions like walking, running, or climbing stairs[44].

For each level of amputation, a wide range of commercially available prosthetic components are designed to replicate lost anatomical functions, including bionic elbows, wrists, hands, knees, ankles, and feet. Depending on individual needs and lifestyle, non-anthropomorphic prostheses are also available. These include specialized tools such as monoarticulated grippers for improved grip efficiency or blade-style prosthetic feet that optimize gait and athletic performance.

Attachment

The conventional clinical approach for attaching a prosthesis relies on a custom-fitted socket, which remains in place by compressing the soft tissue around the residual limb (*Figure 3, left*). While this approach provides a relatively stable, non-invasive mechanical attachment of the prosthesis, it is often associated with complications. The continuous external pressure from the socket on the skin of the residual limb can lead to a range of adverse effects, including, but not limited to, redness, blisters, sweating[45], or even more severe dermatological issues[46].

Moreover, individuals with short residual limbs or anatomically challenging limb shapes often require auxiliary suspension mechanisms to ensure a secure prosthetic fit (*Figure 3, right*). For example, those with proximal transhumeral amputation or shoulder disarticulation commonly use a harness system that wraps around the upper body to stabilize the prosthesis. This is necessary because a short residual limb provides limited surface area for socket attachment, compromising stability. However, while these auxiliary suspension systems enhance retention, they can also cause discomfort and significantly restrict the user's range of motion during prosthesis use[47].

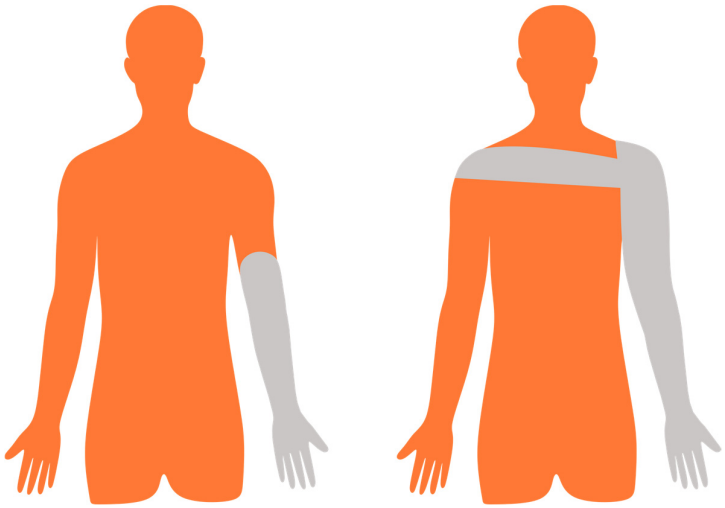

Figure 3. *Conventional mechanical attachment of a prosthesis using a socket (left) and the combined use of a socket and harness for individuals with short residual limbs (right).*

Control

Prosthetic control strategies vary depending on the type of device. For example, body-powered prostheses are operated mechanically, using force transmitted through cables and a harness system[48]. In contrast, myoelectric prostheses rely on decoding electrical signals generated by muscle contractions, called electromyography (EMG) signals. These signals originate from the depolarization of muscle fiber membranes during activation. By selectively contracting specific muscles, users can produce distinct myoelectric signals corresponding to intended movements.

However, the range of controllable actions depends heavily on the availability of functional muscle tissue. In more proximal limb loss, such as transhumeral amputation or shoulder disarticulation, signal sources are limited, typically restricted to the remaining portions of the biceps and triceps or the thoracic region. This reduction in muscle mass significantly narrows the control options for myoelectric devices. Beyond muscle signals, alternative control sources include direct neural interfaces, which tap into peripheral nerves[49], or brain-computer interfaces[50], which decode signals directly from the central nervous system to control the prosthesis. These approaches remain less commonly used methods of prosthetic control following limb loss.

The conventional method for capturing myoelectric signals involves surface electrodes placed on the skin overlying the muscle. However, these electrodes are inherently separated from the neuromuscular source by layers of biological tissue, which act as volume conductors that capture a composite signal from surrounding muscle activity. The quality and specificity of these signals are affected by factors such as muscle depth, tissue thickness, and the size, shape, and placement of the electrodes[51, 52]. Additionally, signal interference from neighboring muscles can complicate interpretation[53]. While surface electrodes offer a non-invasive solution for recording muscle activity, they are prone to electromagnetic interference and shifting during prolonged use, resulting in unstable signal quality and reduced selectivity in detecting specific muscle contractions[54, 55].

Prosthetic control is also influenced by the available myoelectric sources, the choice of sensors for capturing muscle signals, and the choice of control strategy. The most common clinical control strategy is direct control, which establishes a simple one-to-one mapping between the electrical activity of a specific muscle and the actuation of a bionic joint. When the mean absolute value of a myoelectric signal exceeds a threshold, the corresponding joint is activated. Because of this direct link, the number of independently controlled joints is limited by the number of viable muscles post-amputation[56]. A more recent commercially available alternative is pattern recognition, which uses machine learning algorithms to decode intended movements from complex muscle activation patterns. These outputs can be mapped either to individual joints or to predefined grasps, such as pinching. The success of pattern recognition depends on the distinctiveness of the muscle patterns, whether intuitive or non-intuitive, to reliably decode motion intent[56, 57].

Sensory Feedback

A key remaining challenge in limb restoration is somatosensory feedback, which is the ability to sense the body-environment interactions. Sensors capture the state of the prosthetic limb, such as joint position (proprioception) or contact forces during object manipulation, and convert this information into stimulation patterns that evoke sensory perception, helping users better control and feel the prosthesis as part of their body[58]. Artificial or supplementary feedback is typically delivered through sensory substitutions and generally falls into two categories: non-invasive (extradermal) and invasive (subdermal). Non-invasive methods, such as mechanotactile[59], vibrotactile[60], or electrotactile stimulation[61], activate mechanoreceptors beneath the skin, for example, by using skin vibrations to signal grip force. However, this feedback is perceived at the residual limb, not the missing limb, making it feel non-intuitive. In contrast, invasive approaches involve neural interfaces that directly stimulate residual neural pathways originally responsible for conveying sensory input from the lost limb to the brain. While promising, this is typically achieved through electrical stimulation, which often lacks the sensation of natural touch[62].

2.2 Limitations with Current Clinical Solutions

The four key areas of artificial limb replacement are advancing at different rates, each corresponding to a distinct technology readiness level (TRL)[58]. However, a major bottleneck in artificial limb replacement is the limited high-resolution, bidirectional communication between the user and the prosthesis. This constraint affects both motor control (from the user to the prosthesis) and sensory

feedback (from the prosthesis back to the user). As a result, even though advanced prosthetic limbs with multiple degrees of freedom (DoF) are commercially available, the restricted number of communication channels limits the number of distinct, controllable movements. This limitation, combined with a lack of reliability, has led many users to abandon advanced prosthetic devices in favor of simpler, more dependable alternatives[63–65].

CHAPTER 3

Advanced Surgical Solutions

Given the relatively low efficacy and significant limitations of conventional clinical solutions, researchers have proposed alternative approaches, often involving surgical procedures. One such method is osseointegration, which allows for the direct skeletal anchorage of the prosthesis. Furthermore, transected nerves are now often redirected to new target muscles for both control and sensory purposes. These surgical innovations are advancing rapidly and are increasingly recognized as critical to the future of prosthetic care.

3.1 Attachment of Artificial Limbs Through Osseointegration

The concept of osseointegration has paved the way for the direct skeletal attachment of prostheses. Osseointegration is defined as the direct structural and functional connection between an implant surface and bone tissue[66, 67]. It was first discovered in the early 1950s by Dr. Per-Ingvar Brånemark in Gothenburg, Sweden. Originally developed for dental implants[68], the concept was expanded in the 1990s to artificial limb replacement, leading to the creation of the Swedish OPRA (Osseointegrated Prostheses for the Rehabilitation of Amputees) implant system. This system consists of three main components, including the titanium threaded fixture that is inserted into the bone, the abutment which is fixated into the fixture extending percutaneously through the skin, and the abutment screw that secures the abutment to the fixture[69] (*Figure 4*).

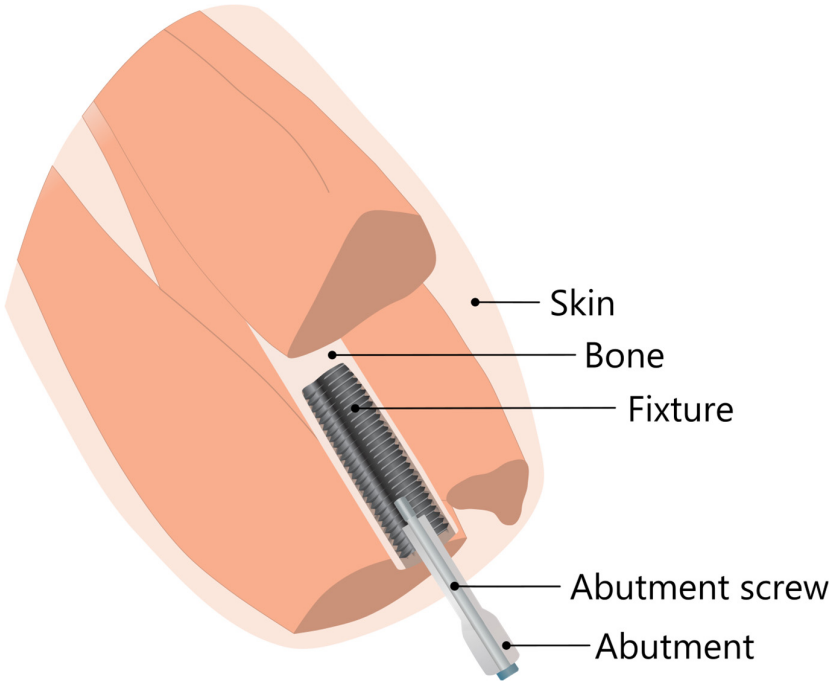

Figure 4. *Illustration of the bone-anchored OPRA (Osseointegrated Prostheses for the Rehabilitation of Amputees) implant system. The system consists of a threaded titanium fixture implanted intramedullary within the bone, a percutaneous abutment press-fitted into the distal end of the fixture, and an abutment screw that secures the abutment to the fixture.*

Bone-anchored prostheses offer a solution to the drawbacks of attaching artificial limbs using conventional suspended sockets. Compared to fitting a limb socket prosthesis over soft tissue, osseointegration enables skeletal fixation, providing a more comfortable and efficient mechanical coupling for transferring loads between an artificial limb and the human body[70]. Furthermore, bone-anchored attachment improves mobility, prosthesis usage, range of motion, comfort while sitting, awareness through osseoperception, and reduces amputation- and prosthesis-related complications, ultimately leading to an improved quality of life (*Table 1*)[69, 71–74].

However, the technique has its limitations (*Table 1*). The rehabilitation process for a percutaneous osseointegrated implant can take 12 to 18 months, depending on the implant design, level of amputation, and the patient's bone quality[18]. The standardized treatment with the OPRA implant system involves a two-stage surgical procedure followed by a structured rehabilitation program, which includes training with a short training prosthesis before gradually increasing prosthetic activity[18, 69]. Various companies have since developed alternative osseointegrated implant systems incorporating different design strategies[70, 75]. While some systems allow for a one-stage surgical procedure, the overall healing period and gradual loading process remain similar[70, 75]. In general, rehabilitation with an osseointegrated prosthesis is physically and mentally demanding for the patient. Additional limitations of this surgical approach include the need for daily hygiene routines to maintain a healthy skin-implant interface, and the presence of a visible transcutaneous metallic component, which may be considered aesthetically undesirable. Furthermore, the implant system is not suitable for high-impact activities such as running or jumping.

Risks and undesirable clinical outcomes associated with bone-anchored percutaneous implants include mechanical complications such as fractures of the implant or other components, superficial or deep infections, soft tissue revisions, implant loosening, and implant removal (*Table 1*). The most commonly reported complications involve mechanical issues with the abutment or abutment screw[76]. In contrast, deep infections and implant removals are relatively rare[69, 76, 77]. Notably, both the incidence of mechanical complications and the risk of infection are lower in the upper limb compared to the lower limb[76, 78]. A recent study with a 15-year follow-up of 111 transfemoral OPRA patients found that 55% experienced mechanical complications requiring abutment or screw replacement. However, severe complications, including 18 implant failures (7 infections, 6 aseptic loosening, 5 fractures), were less common. Despite these issues, long-term outcomes with bone-anchored prostheses were significantly better than with socket-suspended prostheses[76].

***Table 1**. Advantages, limitations, and risks associated with bone-anchored osseointegrated prostheses.*

Advantages	No skin irritation from mechanical friction No residual limb compression Temperature-independent Suitable for short or anatomically challenging residual limbs Easier donning and doffing Full range of joint motion Osseoperception
Limitations	Prolonged rehabilitation process Requires daily hygiene maintenance Less aesthetically appealing Not suitable for high-impact activities
Risks	Implant or component fractures Superficial or deep infections Soft tissue revision surgeries Implant loosening Implant removal

3.2 Selective Nerve Transfers and Muscle Reconstruction

Selective nerve transfers and muscle reconstruction are used in both biological and bionic limb reconstruction to enhance function by improving motor control and sensory feedback.

Surgical Techniques for Enhancing Efferent Neural Interfaces

One of the earliest surgical techniques developed to enhance intuitive prosthetic control is Targeted Muscle Reinnervation, introduced in the early 2000s by Dr. Todd Kuiken and Dr. Gregory Dumanian at Northwestern University in Chicago, USA[21, 79–81]. TMR involves rerouting severed peripheral nerves to nearby, functionally redundant muscles in the residual limb. These target muscles are first denervated to allow their muscle fibers to be reinnervated. Once reinnervated, they serve as biological amplifiers of motor intent, generating new EMG signals that can be used as additional control sources for myoelectric prostheses. TMR enables intuitive control of up to three DoF using EMG amplitude-based signals[82] and is currently the most widely adopted surgical reconstruction technique for individuals with limb amputation[83].

Some concerns with the TMR technique include significant size mismatches between donor and target nerves, the denervation of remaining functional muscles, and the limited number of newly created myoelectric sites. To address these limitations, a research group at University of Michigan in the USA, led by Professor Paul Cederna, developed an alternative approach known as the Regenerative Peripheral Nerve Interface[28, 29]. Like TMR, RPNI uses muscle tissue to biologically amplify motor nerve signals but allows for control of a greater number of prosthetic joints. In this technique, free muscle grafts harvested from other parts of the body serve as targets. Instead of transferring an entire nerve to a single large muscle, the nerve is longitudinally dissected into individual fascicles, each implanted into a separate muscle graft that is wrapped around the nerve stump. This approach has been shown to generate additional myoelectric signals suitable for prosthetic control[22, 30]. However, because the muscle grafts used in RPNIs are significantly smaller than the target muscles in TMR, capturing signals with surface EMG electrodes poses a challenge. Other RPNI variants have been developed, including muscle cuff RPNI (MC-RPNI)[84] and composite RPNI (C-RPNI)[85], though to date, only feasibility in animal models has been demonstrated.

To address concerns with RPNIs, including ensuring sufficient vascularization of the muscle grafts, an intermediate approach was developed by Dr. Sami H. Tuffaha's group at Johns Hopkins University in Baltimore, USA. This method lies between transferring nerves to a native denervated muscle (as in TMR) and implanting free muscle grafts (as in RPNI). It involves dissecting a portion of native muscle, severing its innervation while preserving its blood supply, thereby creating a Vascularized Denervated Muscle Target (VDMT). Early findings suggest that VDMTs may help reduce postamputation pain, although they have not yet been applied for prosthetic control[86]. In animal studies, researchers have also explored splitting muscles to generate additional myoelectric signals[87]. The drive to increase both the number and quality of these signals through progressively refined surgical techniques continues to fuel advancements in surgical human–machine interface research.

Surgical Techniques for Enhancing Afferent Neural Interfaces

Surgical techniques have also been employed to restore somatosensory perception in individuals with limb loss. This concept was initially discovered incidentally during TMR[21], but was later intentionally developed into a dedicated approach known as Targeted Sensory Reinnervation (TSR). TSR involves the surgical transfer of residual sensory nerves to new skin areas in the residual limb, and has been successfully demonstrated in individuals with both upper and lower limb amputations[88–91]. When the reinnervated skin is touched, individuals often experience referred sensations perceived as originating from the missing limb. Although the resulting sensory maps are highly variable and frequently disorganized[92], the sensations are often described as natural, something rarely achieved through direct electrical stimulation[93].

Moreover, the Agonist-Antagonist Myoneural Interface (AMI) is a novel surgical technique developed by Professor Hugh Herr's group at the Massachusetts Institute of Technology in Boston, USA. It is designed to restore proprioception after limb loss by reconnecting residual agonist-antagonist muscle pairs via artificial anchoring points[94]. When one muscle contracts, its opposing muscle stretches, activating afferent signals from muscle spindles and Golgi tendon organs to convey joint position and force. AMI has been implemented in humans, primarily in individuals with lower limb amputation using native muscles, and combined with EMG-based control to enable closed-loop prosthetic ankle function[95]. However, its additional clinical benefits remain uncertain, as near-normal neuromechanics can often be achieved through direct EMG control and training without requiring further surgery[96].

Several proposed sensory or sensorimotor interfaces remain in the experimental stage, having been tested primarily in animal models. The RPNI group introduced the dermal sensory RPNI (DS-RPNI), which involves wrapping nerve fascicles in autologous dermal grafts instead of skeletal muscle[97]. Meanwhile, the Boston group has proposed regenerative AMIs, based on principles similar to RPNIs. Although promising in animal studies, it remains unclear whether reinnervated muscle grafts can consistently generate the forces necessary to evoke proprioception. This group also developed the cutaneous mechanoneural interface (CMI)[98], which uses a muscle-actuated skin flap to elicit haptic feedback, though it remains in early-stage testing. Additionally, Professor Oskar Aszmann's team at the Medical University of Vienna in Vienna, Austria, recently proposed a biological sensorimotor interface integrating motor control and sensory feedback, demonstrating successful reinnervation of target muscles by efferent fibers and skin grafts by afferent fibers in animal studies[99].

As outlined in the previous sections, surgical strategies for residual limb reconstruction have gained significant momentum over the past two decades, with TRLs ranging from early conceptual stages to well-established clinical practice. An overview of the TRL for each approach is presented in *Figure 5*.

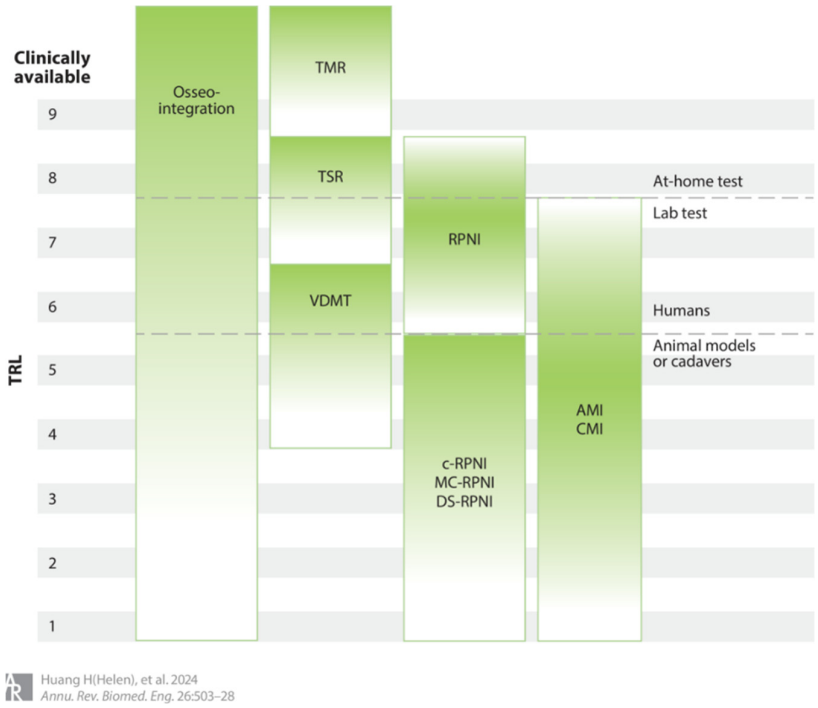

Figure 5. *Technology Readiness Levels (TRLs) of surgical techniques for neural prosthetic interfaces. Each bar illustrates the TRL range for a specific surgical technique based on the current state of research. Darker shading represents a greater volume of published studies at that TRL, indicating a higher degree of development and validation. The vertical axis denotes the TRL scale, ranging from early-stage conceptualization to full clinical implementation. The figure is taken from Huang et al.*[58]

3.3 Combining Surgical Solutions with Engineering Approaches

The osseointegrated implant system has been further enhanced to incorporate implanted electrodes interfacing with residual muscles and nerves. This enhancement enables intuitive control through EMG signal decoding and allows for somatosensory feedback via direct nerve stimulation (*Figure 6*)[47]. This bidirectional system, known as the neuromusculoskeletal interface, leverages the percutaneous implant as a conduit for transmitting signals between the prosthetic limb and the user's nervous system. A key advantage of this approach is that all active electronics, such as the stimulation and recording systems, are located outside the body, thereby reducing potential risks to the user.

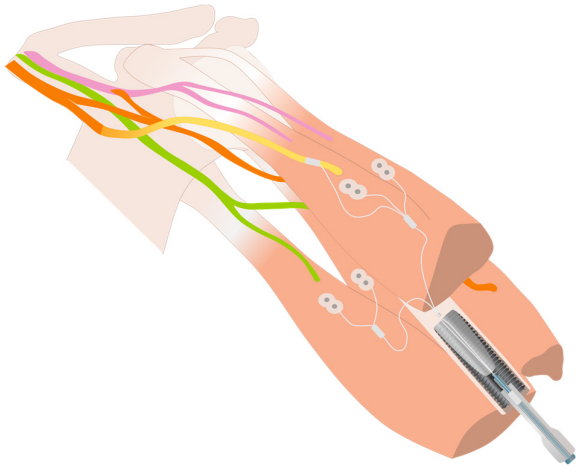

Figure 6. *Neuromusculoskeletal interface, including bone-anchored implant and electrodes connected to the muscles and nerves, allowing for motor control and somatosensory feedback.*

Additionally, the neuromusculoskeletal interface has been integrated with surgical advancements to expand the number of usable myoelectric signal sources for prosthetic control[100–102]. When combined with TMR, the interface enables control of multiple DoF, increasing from one to two or three (*Figure 7A*)[100]. This enhancement allows individuals with transhumeral amputation to reliably control elbow flexion/extension, wrist pronation/supination, and hand opening/closing. Moreover, by incorporating both TMR and RPNI with advanced decoding algorithms, researchers have achieved impressive outcomes, including single-finger control in a person with transhumeral amputation (*Figure 7B*)[102].

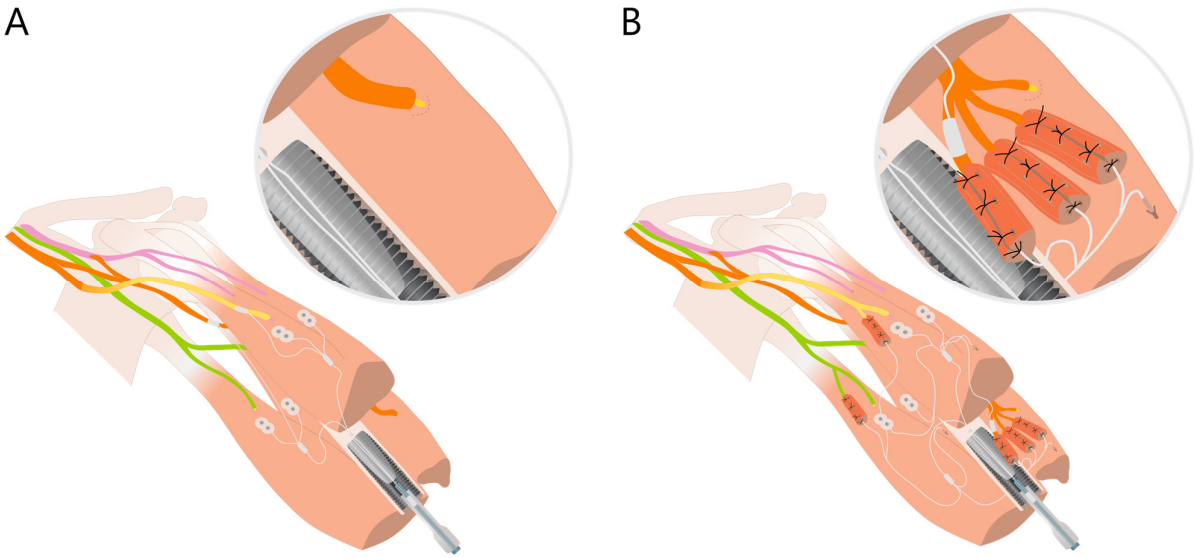

Figure 7. *Neuromusculoskeletal interface combined with advanced surgical techniques, including (A) Targeted Muscle Reinnervation (TMR), and (B) TMR in combination with Regenerative Peripheral Nerve Interface (RPNI).*

CHAPTER 4

Enhancing Osseointegration Using Electrical Stimulation

It has been suggested that successful use of an osseointegrated prosthesis depends on the rapid formation, proper maintenance, and infection-free status of the bone–implant interface[103]. Inadequate osseointegration is a major cause of implant failure and may ultimately necessitate implant removal[70]. Gaps or pockets at the bone-implant interface that fail to integrate pose a risk for bacterial colonization and biofilm formation, potentially leading to severe infections even years after implantation[104]. Another critical consequence is implant loosening, where insufficient anchorage in the bone prevents the implant from functioning properly[105]. As discussed previously, the osseointegration process typically spans several months and may extend up to 1.5 years, depending on implant design and bone quality. In scenarios requiring early loading or where bone quality is compromised, strategies to accelerate osseointegration are highly desirable to improve outcomes and reduce complications[106, 107].

Extensive research has focused on enhancing the biological bonding between implants and bone tissue. Efforts have included the development of surface modifications, optimization of implant morphology and materials, and refinement of surgical implantation techniques[108–110]. In this context, we conducted a literature review of studies investigating electrical stimulation as a means to promote osseointegration, with a focus on stimulation parameters (*Paper I*[37]). Particular attention was given to studies that employed the implant itself as a stimulating electrode, used titanium as the implant material due to its corrosion resistance and mechanical strength, and evaluated the isolated effects of electrical stimulation, excluding studies that combined it with other modalities such as mechanical loading.

4.1 Electrical Stimulation to Accelerate Osseointegration

When using electrical stimulation to promote osseointegration, several factors must be considered regarding its delivery, including electrode configuration, the type of stimulation source, and stimulation parameters.

The placement of electrodes significantly influences the resulting electric field. Stimulation can be classified as exogenous, where the implanted fixture acts as an electrode and additional electrodes are placed externally on the skin, or endogenous, with electrodes positioned internally within the body. Electric current may be delivered as direct current (DC), characterized by a steady magnitude and direction; alternating current, with periodic polarity reversals or varying magnitude; or pulsed current, consisting of short bursts of electrical events. Pulsed currents are composed of isolated pulses, either unidirectional or bidirectional, separated by intervals of no current flow. These pulses, measured in Hertz (Hz), can be shaped into various waveforms[111]. A pulse may have a monophasic waveform, appearing above the zero baseline with positive polarity, or a biphasic waveform, crossing the baseline symmetrically or asymmetrically. To prevent net charge accumulation, pulses are often charge-balanced. Key stimulation parameters, including amplitude (μA), pulse width (μs), frequency (Hz), inter-phase delay (μs), and duty cycle (%), influence the electric field and can significantly impact outcomes, including the risk of adverse effects.

The review identified DC stimulation as the predominant method employed in both *in vitro* and *in vivo* studies. It has demonstrated positive effects on osteoblast activity and has been associated with improved bone-implant integration[103]. However, despite these benefits, several limitations have been identified. One issue is the accumulation of charged proteins at the electrode surface with opposite polarity, which can impede current flow and lead to inconsistent stimulation of target cells[112]. Furthermore, DC stimulation has been reported to induce the formation of reactive oxygen species (ROS), such as hydroxyl radicals, hydrogen peroxide, and other free radicals[113], agents known to contribute to bone resorption[114]. Another concern is the potential increase in pH of the surrounding environment, which may create cytotoxic conditions[112].

Pulsed current stimulation was introduced in the early 2000s to overcome several limitations of DC stimulation. One of the pioneering studies by Kim *et al*. investigated the use of biphasic (charge-balanced) electrical pulses to minimize net charge accumulation during cell exposure[112]. Their *in vitro* study demonstrated that biphasic stimulation promoted cell proliferation and increased the expression of vascular endothelial growth factor, a key marker of angiogenesis. However, the study did not evaluate changes in pH or ROS levels. Building on their *in vitro* findings, the group further evaluated biphasic electrical stimulation in a canine mandibular model, applying parameters derived from their earlier experiments. After three weeks, they observed a significant increase in both bone area and bone-to-implant contact in the stimulated specimens[106].

Review Key Findings

The review identified several important aspects:

- Electrical stimulation appears to promote osseointegration in both *in vitro* and *in vivo* models.
- Pulsed electrical stimulation may mitigate several limitations inherent to DC stimulation.
- Optimal stimulation parameters are not well defined, underscoring the need for further research.
- Key parameters that significantly affect the outcomes include amplitude, frequency, stimulation duration, and protocol.
- There is a lack of clinical studies in humans, therefore, its efficacy in clinical settings remains untested.
- Reporting standards are inconsistent, with many studies failing to justify their choice of stimulation parameters or to report them comprehensively.

4.2 Introducing a Novel Stimulation Concept

Building on insights from the literature review, the design of the neuromusculoskeletal interface, and established safe stimulation paradigms for sensory feedback via nerve stimulation, we proposed a novel electrical stimulation approach. Instead of connecting a prosthesis to the abutment, this concept involves connecting the osseointegrated implant to an electrical stimulator capable of delivering targeted stimulation according to a specific treatment paradigm. The approach utilizes the same asymmetric biphasic pulse commonly employed in peripheral nerve stimulation, with the implant serving as the cathode and electrodes connected to nerves and muscles acting as the anode (*Figure 8A*). Alternatively, when only the bone-anchored implant is available, exogenous surface electrodes serve as the anode (*Figure 8B*).

This stimulation approach has not been previously tested for promoting osseointegration, and optimal pulse parameters remain undefined. To address this, we developed an *in vitro* model to deliver pulsed electrical stimulation and assess its effects on bone cells (*Paper II*[38]).

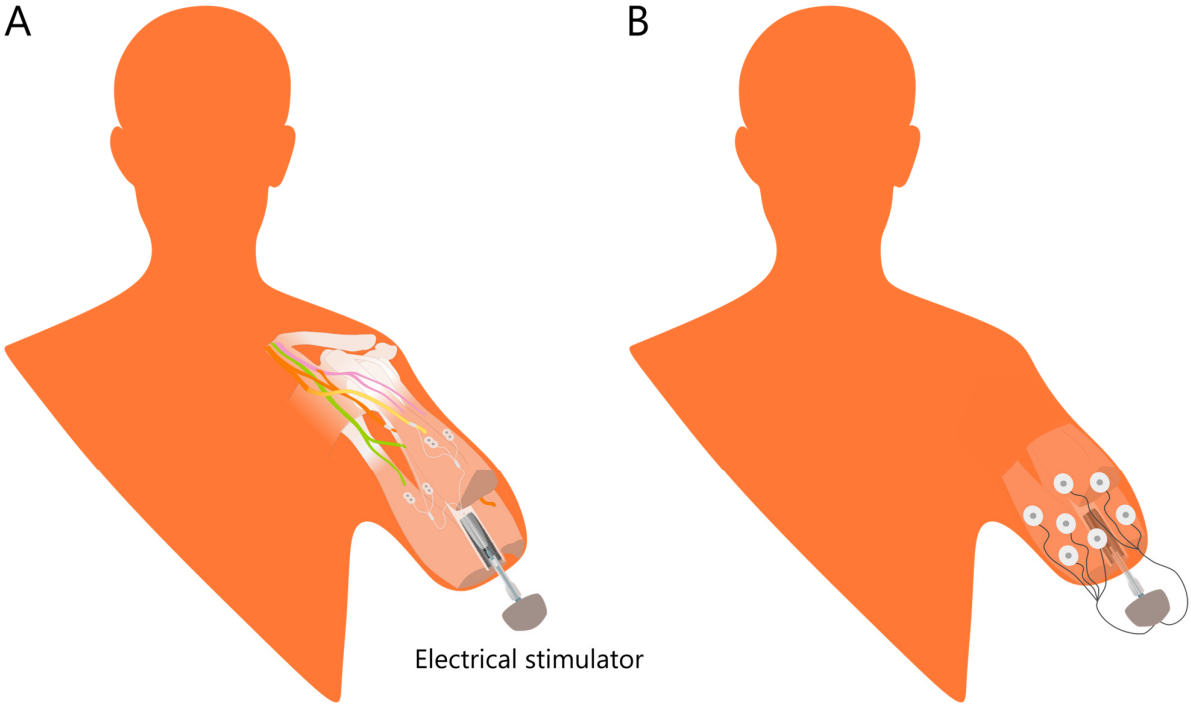

Figure 8. *Conceptual illustration of delivering electrical stimulation to promote osseointegration. The bone-anchored implant serves as the cathode and is connected to an electrical stimulator. Stimulation is delivered using either implanted electrodes within the neuromusculoskeletal interface as anodes (A) or surface electrodes as anodes (B).*

Design and Execution of In Vitro Study

We designed an experimental setup to mimic the neuromusculoskeletal interface using a simplified model. The setup consisted of a Ti6Al4V plate, mimicking the implant fixture and serving as the cathode and two Ti6Al4V discs functioning as anodes, all housed within a 3D-printed chamber. These components were connected to a bipolar constant current generator and an arbitrary function generator, which delivered electrical pulses *(Figure 9)*. The electrical stimulation consisted of charge-balanced, cathodic, rectangular, biphasic asymmetric (10:1), current-controlled pulses (*Figure 9*). The cathodic phase (negative pulse) was followed by an inter-pulse break (zero amplitude) and a recovery phase (positive pulse) that was 10 times smaller in amplitude and 10 times longer in duration than the cathodic phase. Each stimulation pulse was followed by a charge recovery phase where any residual charge was recovered back to zero to ensure that charge accumulation could not occur.

The implants, pre-cultured with MC3T3-E1 preosteoblasts, were continuously stimulated for 72 hours at two pulse amplitudes (10 µA and 20 µA) and two frequencies (50 Hz and 100 Hz)[38]. Fixed pulse parameters included negative pulse width (500 µs), interpulse break (50 µs) and sample frequency (100 kSPS). After 72 hours, the stimulated groups were compared to an unstimulated control group regarding cell distribution, morphology, viability, soluble collagen production, and pH levels.

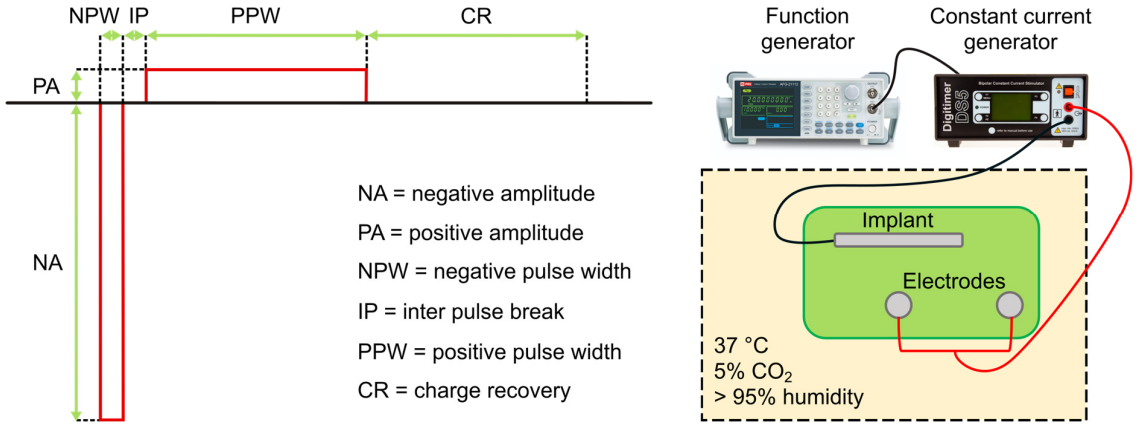

Figure 9. *Characteristics of the stimulation pulses (left). Schematic of the electrical circuit, where the implant serves as the cathode and the electrodes act as anodes, connected to a constant current generator, which is controlled by a function generator (right).*

Results and Conclusion of In Vitro Study

Assessments revealed no significant pH difference between the control and the stimulated groups ($p > 0.05$). Additionally, no morphological alterations were observed after 72 hours of pulsed electrical stimulation. In the preculture group (16 hours before stimulation), MC3T3-E1 cells displayed an elongated morphology (*Figure 10A–C)*. Following 72 hours of stimulation, cells adopted a more flattened morphology (*Figure 10E, H, K*), with increased cell density noted in the A20F50 and A20F100 groups compared to A10F50 (*Figure 10*D, *G, J*). All stimulated groups (A10F50, A20F50, A20F100) demonstrated the presence of extracellular matrix-like structures, with the A20F50 group exhibiting the highest density (*Figure 10F, I, L*).

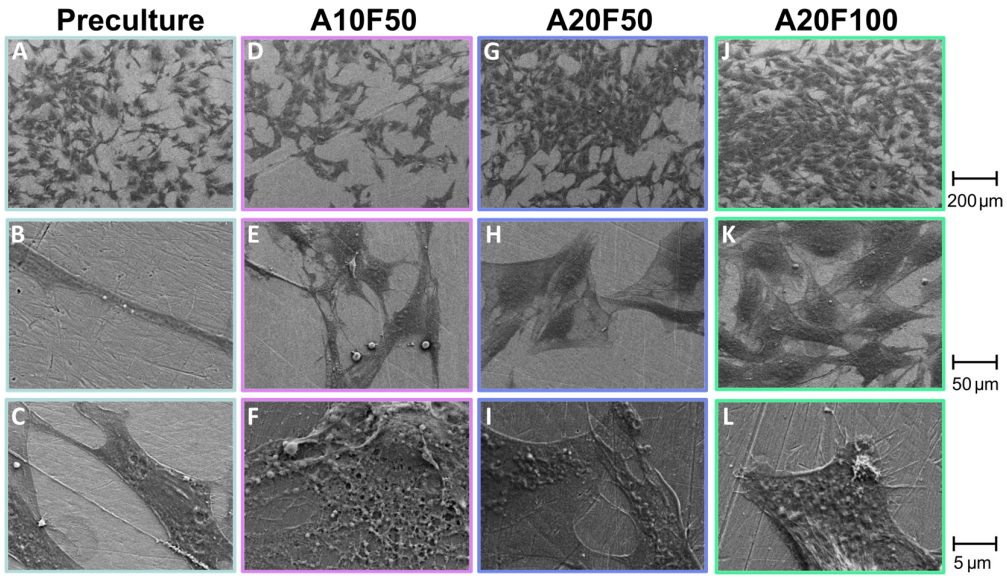

Figure 10. *MC3T3-E1 preosteoblast morphology observed via scanning electron microscopy. (A–C) Cells precultured on Ti6Al4V for 16 hours prior to electrical stimulation. (D–L) Cells after 72 hours of pulsed electrical stimulation under varying amplitude and frequency conditions: (D–F) A10F50, (G–I) A20F50, and (J–L) A20F100.*

Pulsed electrical stimulation enhanced both cell viability and collagen production. Compared to the control group (*Figure 11A*), cell viability was significantly increased in A10F50 ($p < 0.05$), A20F50 ($p < 0.008$), and A20F100 ($p < 0.001$). No significant differences were found between groups stimulated at 50 Hz (A10F50 vs. A20F50) or at 20 µA (A20F50 vs. A20F100), though A20F100 showed significantly higher cell count than A10F50 ($p < 0.05$) and even exceeded the baseline (0 h). Collagen production was also significantly increased in A20F50 ($p < 0.04$) and A20F100 ($p < 0.001$) compared to the control group, but not in A10F50 ($p > 0.05$) (*Figure 11*B). A20F100 exhibited the highest collagen levels, with a significant difference compared to A10F50 ($p < 0.001$). However, no statistically significant differences were observed between groups at 50 Hz ($p = 0.0873$) or 20 µA ($p = 0.0979$).

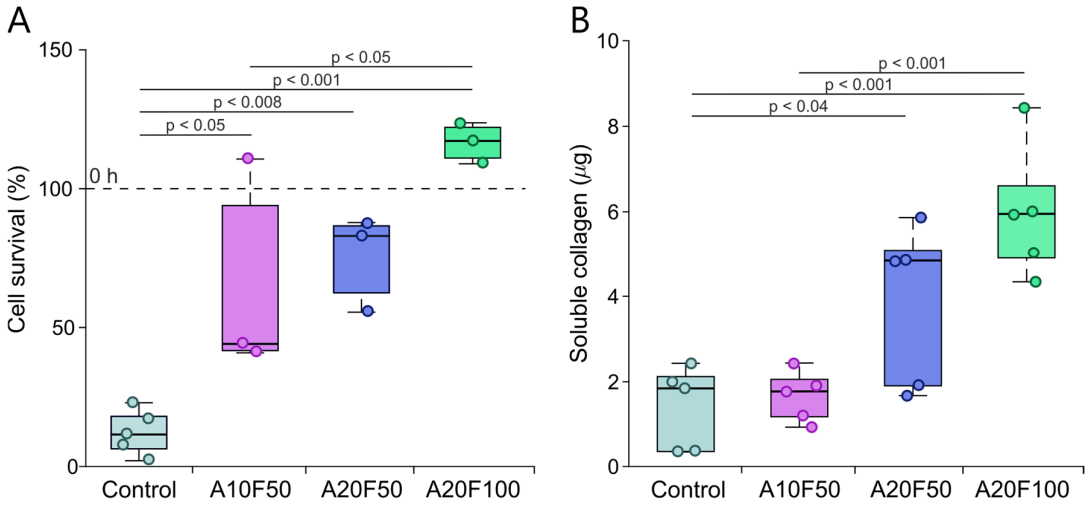

Figure 11. *MC3T3-E1 cell survival at 72 h (A) and collagen production at 72 h (B).*

In this preliminary *in vitro* study, we demonstrated that applying pulsed electrical stimulation using the same waveform employed in peripheral nerve stimulation for sensory feedback shows promise as a modality to enhance osseointegration. However, identifying the optimal stimulation parameters remains a key challenge. Our findings indicate that both pulse amplitude and frequency significantly influence the biological response, underscoring the importance of parameter selection. As previously discussed, pulsed electrical stimulation introduces a greater number of variables than continuous stimulation, such as pulse width, duration, and duty cycle, which must be systematically investigated and optimized.

In conclusion, these preliminary results suggest that this stimulation approach may have clinical potential to accelerate osseointegration or facilitate re-osseointegration in cases of implant failure. Nevertheless, further comprehensive studies, both *in vitro* and *in vivo*, are essential to validate these findings and refine the protocol for clinical translation.

CHAPTER 5

Postamputation Pain

Following major limb loss, pain is a major challenge many individuals face, which is often more difficult to treat due to its complex and multifactorial origins. The term “postamputation pain” is commonly used as an umbrella term encompassing the various types of pain associated with amputation.

5.1 Phantom Phenomena

After major limb loss, individuals often perceive the missing limb as if it were still present[115, 116]. This occurrence is known as “phantom phenomena” or “phantom limb” and was first coined in 1872 by Silas Weir Mitchell[117, 118]. However, the earliest accounts of phantom phenomena trace back to the mid-16th century, when a French military surgeon observed that amputated soldiers continued to perceive sensations from their missing limbs[119]. Phantom phenomena are generally divided into non-painful and painful referred sensations[120]. Phantom limb sensations (PLS) refer to the non-painful somatosensory experiences related to the missing limb, including touch-like (e.g., tingling), proprioceptive-like (e.g., perceived limb positions or movements), and temperature-like sensations. The phantom limb may also appear distorted in shape, size, or position (e.g., telescoping)[116] (*Figure 12*). The incidence of PLS after major limb loss is up to 98%[121].

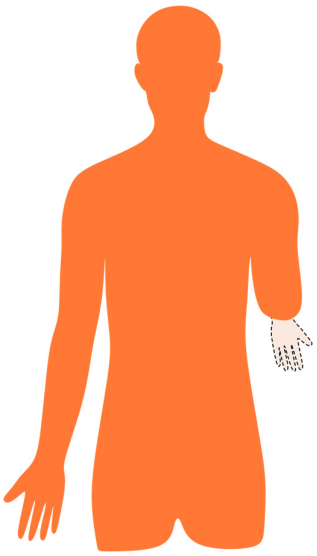

Figure 12. *Phantom limb sensations can manifest as telescoping, where the phantom hand appears retracted into the residual limb, and in this illustration also distorted in size.*

Phantom limb experiences can feel as vivid and real as sensations from an intact limb. Individuals with limb loss have described using their phantom hand to shake hands, hold a cup of coffee, or gesture during conversation[120]. These sensations are highly subjective and can seem illogical, disappearing and reappearing within minutes or hours, shifting spontaneously in position, or becoming stuck in awkward or painful postures. Despite their unpredictability, phantom limb sensations are often perceived as welcome and natural[116].

Moreover, phantom phenomena have been reported in other patient groups with deafferentation, including those with brachial plexus and spinal cord injuries[115, 122]. Similar experiences have also been observed following the surgical removal of body parts other than limbs, such as the breast, nose, and even internal organs[123–125].

5.2 Residual Limb Pain and Phantom Limb Pain

The International Association for the Study of Pain (IASP) defines pain as "*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.*" Pain can be classified as either nociceptive or neuropathic. According to the IASP, nociceptive pain arises from actual or potential damage to non-neural tissue and is caused by the activation of nociceptors. It serves as a physiological response intended to protect the body by promoting the avoidance of potential or actual injury. In contrast, neuropathic pain results from a lesion or disease affecting the somatosensory nervous system, such as severed nerves following amputation or deafferentation. These disruptions alter normal afferent input to the spinal cord, often leading to maladaptive neuroplastic changes and persistent pain.

Chronic neuropathic pain is a common and challenging consequence of major limb amputation, affecting up to 85% of individuals and severely diminishing their quality of life[3, 117, 126–131]. This type of postamputation pain is complex and multifactorial, typically manifesting as either pain localized to the remaining portion of the limb, referred to as residual limb pain (RLP), or pain perceived in the missing limb, known as phantom limb pain (PLP)[132] (*Figure 13*). RLP can stem from a variety of causes, including inflammation, infection, neuroma formation, heterotopic ossification, bursitis, or musculoskeletal abnormalities[5]. Since sharp or distinct pain triggered by mechanical stimulation of neuromas (e.g., via Tinel's sign test) is common, neuroma pain is often classified separately from RLP. Furthermore, in contrast to known sources of RLP, the mechanisms underlying PLP are less well understood but are thought to involve a dynamic interaction between peripheral nerve injury and central nervous system reorganization[117, 133].

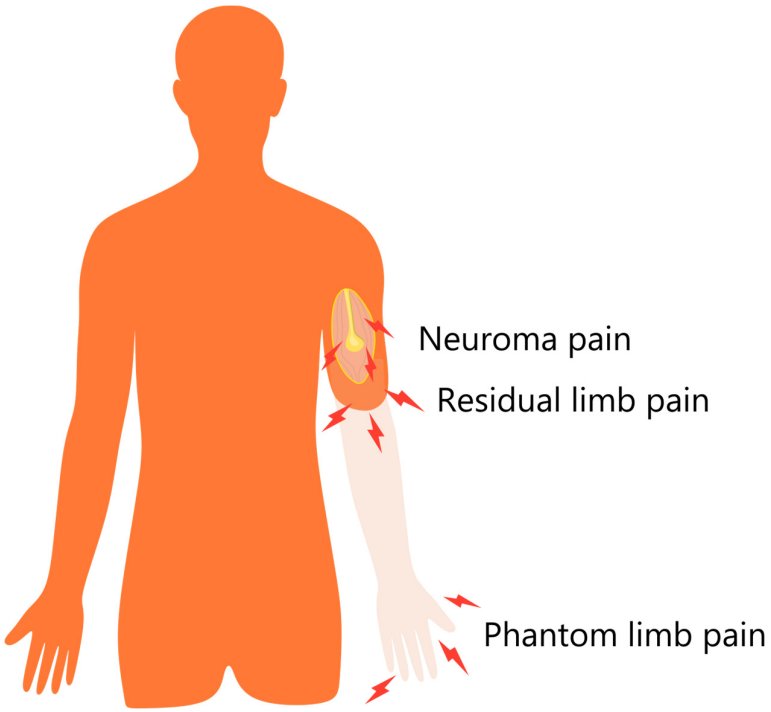

Figure 13. *Illustration of amputation-related pain categorized as neuroma pain, residual limb pain (RLP), and phantom limb pain (PLP). Neuroma pain refers to distinct pain triggered by stimulation of the neuroma. RLP describes painful sensations localized to the residual limb, while PLP refers to pain perceived in the missing body part.*

Mechanisms of Neuropathic Pain: Peripheral and Central Sensitization

After peripheral nerve injury, the proximal nerve stump initiates regeneration, while the distal segment undergoes Wallerian degeneration to clear debris and support axonal regrowth[134] (*Figure 14*). Typically, the regenerating axons attempt to reconnect with their target tissues[135].

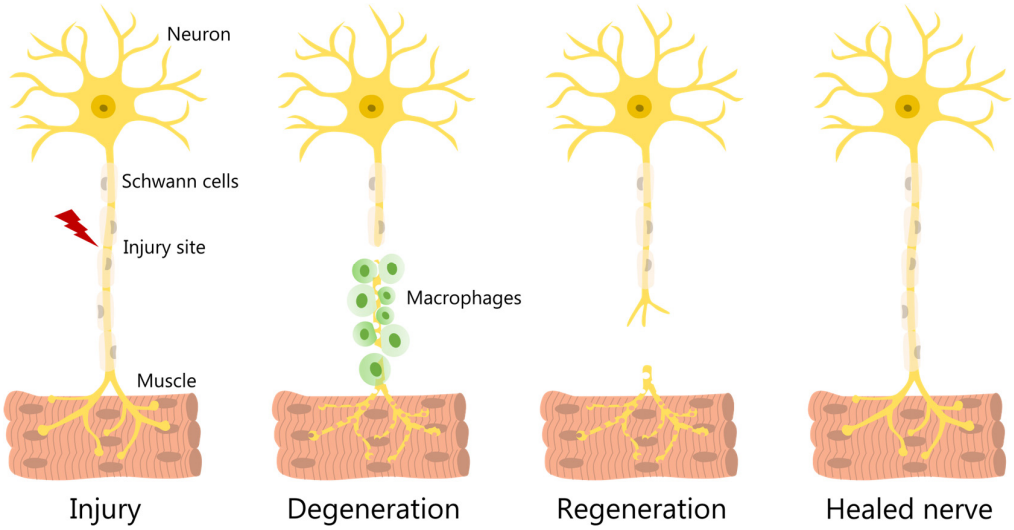

Figure 14. *Schematic illustration of Wallerian degeneration following nerve injury, showing both degeneration of the distal nerve segment and regeneration of the proximal nerve stump.*

However, in the context of amputation, where these targets are absent, axonal regrowth becomes disorganized, leading to sprouting into surrounding scar tissue and the formation of a neuroma (*Figure 15*). Damaged nociceptive fibers within neuromas may develop a lowered activation threshold, causing spontaneous firing even without external stimuli[136]. This process is a key mechanism of peripheral sensitization, where heightened nerve sensitivity leads to exaggerated pain responses[137]. Consequently, individuals may experience hyperalgesia (increased pain from normally painful stimuli) and allodynia (pain triggered by typically non-painful stimuli, such as light touch or brushing of the skin)[138]. Additionally, neuromas release inflammatory cytokines that can alter pain processing in the somatosensory cortex, contributing to maladaptive central nervous system changes and intensifying pain[139, 140]. Chronic pain arises from complex, bidirectional interactions between the peripheral and central nervous systems. Persistent peripheral neuropathy can induce central sensitization, distorting the brain's response to new sensory input[141]. Since neuromas are key contributors to both residual limb pain and phantom limb pain, effective neuroma management is essential for mitigating postamputation neuropathic pain.

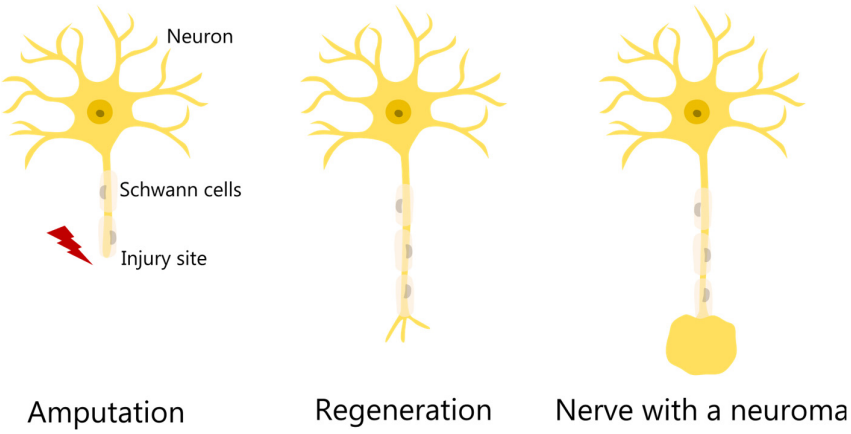

Figure 15. *Schematic illustration of neuroma formation following amputation.*

CHAPTER 6

Surgical Treatments for Postamputation Pain

Historically, surgical treatments were not regarded as superior to non-surgical options for managing postamputation pain[142]. However, recommendations for managing terminal neuromas after amputation have evolved, and today, surgical interventions are frequently employed both to treat and prevent postamputation pain[143].

In the late 1970s, the standard recommendation was to leave the mature neuroma intact and transpose it to a "quiet" location, such as deep within a muscle[144, 145]. By the 1980s, research demonstrated that terminal neuromas generate ectopic signals and are highly mechanosensitive, prompting a shift toward neuroma resection[146–148]. However, a major challenge remained: how to manage the proximal nerve end to prevent regeneration into a new painful neuroma? Over the years, various techniques have been explored to prevent neuroma formation, including freezing the nerve, pharmacologic inhibition, and nerve capping with synthetic materials, biomaterials, or the epineurium[149]. Nevertheless, these approaches have generally not proven effective.

Over the past decade, the treatment paradigm has evolved with the development of surgical techniques that prevent neuroma formation by guiding severed nerves toward appropriate target structures[34, 145]. Surgical strategies for treating and preventing painful neuromas are generally classified as either non-reconstructive ("passive") or reconstructive ("active"). Non-reconstructive methods typically involve neuroma excision without directing the severed nerve toward a physiologically appropriate target, such as bone or an already innervated muscle. In contrast, reconstructive approaches aim to promote healthy nerve regeneration by providing a suitable physiological pathway after neuroma excision.

6.1 Conventional Non-Reconstructive Surgical Treatments

Conventional surgical treatments of terminal neuromas include a wide range of options, including, but not limited to, traction neurectomy alone, transposition with implantation into nearby tissue, closure of the distal nerve end, and neurorrhaphy[34, 150] (*Figure 16*). Various nerve-end manipulation techniques have yielded mixed results in terms of pain relief. For example, traction neurectomy alone has been linked to a high recurrence rate of painful neuromas[151]. Additionally, limited clinical success and anatomical challenges have contributed to the infrequent use of certain methods, such as epineural grafting and centro-central neurorrhaphy[150].

The most common technique involves neuroma excision followed by implantation into nearby tissues such as muscle, bone, or vein. Outcomes of this approach have varied: some patients experience no relief, gradual improvement, or complete pain resolution, while others achieve initial pain relief after surgery but later develop recurrent pain[152, 153]. According to neurophysiological principles, a freshly cut peripheral nerve will undergo axonal sprouting and elongation. Therefore, the main criticism of these passive techniques is that, without appropriate target end organs for reinnervation, this process is likely to result in the recurrence of a painful neuroma[34, 154]. In contrast, the main strategy of these techniques is to remove the freshly transected nerve stump away from possible external pressure, such as a prosthetic socket, to avoid the firing of painful sensations from the neuroma. This strategy

does not address the actual problem, which is the process of neuroma formation; instead, it reduces the likelihood of external stimuli to the neuroma. However, despite its limited success in pain reduction, neuroma excision followed by intra-muscle transposition remains widely used in amputation care. It is still largely considered the "gold standard" for surgically treating painful terminal neuromas[34, 155].

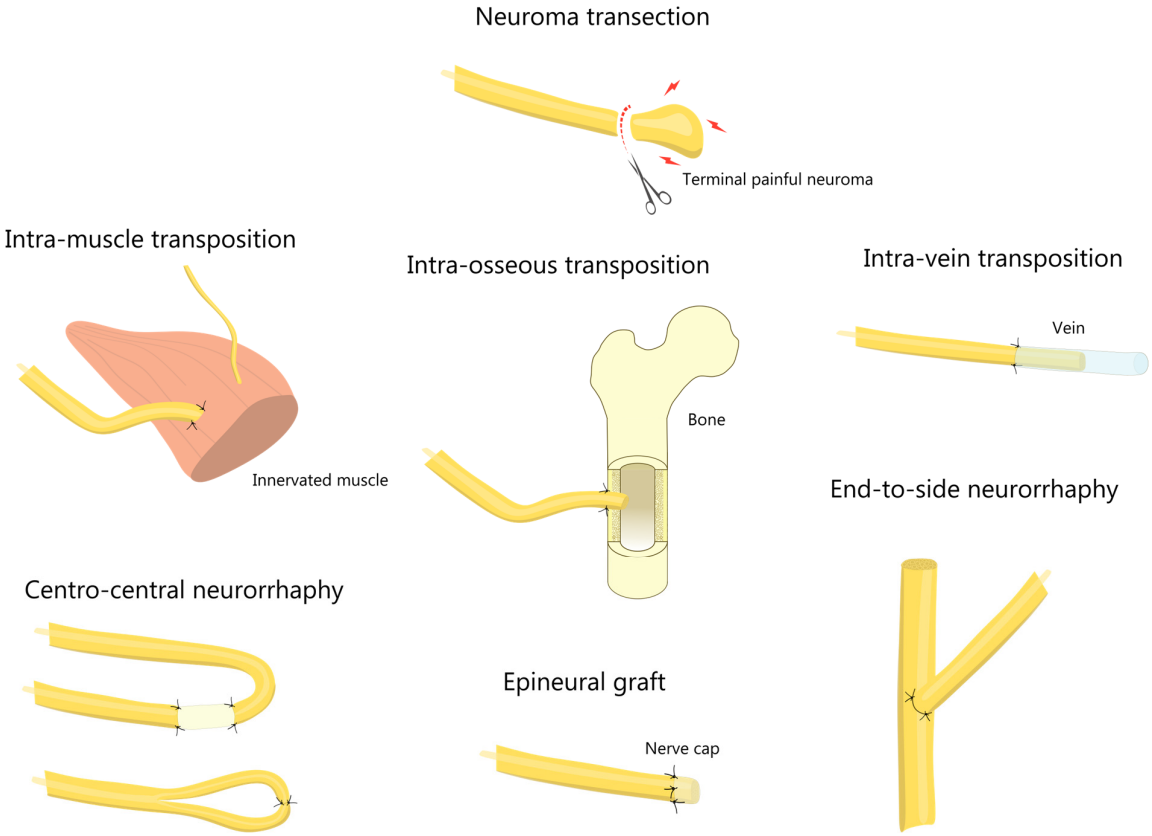

Figure 16. *Conventional non-reconstructive surgical treatments for postamputation pain. Following neuroma transection, options include transposition of the nerve to innervated muscle, bone, or vein, centro-central neurorrhaphy, epineural nerve capping, or end-to-side neurorrhaphy.*

6.2 Proactive Reconstructive Surgical Treatments

Proactive surgical techniques adopt a fundamentally different strategy from non-reconstructive approaches, focusing on the management of the nerve end following transection. These techniques aim to facilitate more natural neuronal regeneration and minimize complications by providing the nerve with a physiologically appropriate target, essentially giving it “somewhere to go and something to do”[156]. A key component of this strategy involves redirecting the severed nerve to denervated tissue, such as muscle or skin, thereby creating a supportive environment for organized regrowth and reducing the risk of painful neuroma formation[143].

One of the earliest and most influential techniques developed in this context is TMR (*Figure 17*). As mentioned in the previous chapter, TMR was initially introduced to enhance intuitive control of myoelectric prostheses. However, TMR yielded an unexpected yet significant secondary benefit: in a cohort of patients treated for functional purposes, 14 out of 15 individuals who previously suffered from neuroma-related pain reported complete pain relief following the procedure[157]. Subsequent research revealed similar benefits from the RPNI technique. Also originally developed to address challenges related to signal amplification and nerve integration, RPNI was later found to significantly reduce both neuroma pain and phantom limb pain, with patients reporting a decreased reliance on analgesics[32]. Over time, both TMR and RPNI have been shown to be effective not only as therapeutic

interventions but also as prophylactic procedures for preventing RLP, and to a lesser extent, PLP[158, 159]. Moreover, newer surgical innovations, some discovered incidentally, like TSR, and others developed to address limitations of earlier techniques, such as VDMT or AMI, have also demonstrated potential efficacy in both the treatment and prevention of postamputation pain[86, 90, 91, 160, 161].

Today, many of these surgical techniques are more commonly utilized for managing postamputation pain than for their original purpose of enhancing prosthetic control. This shift in clinical application underscores the substantial and ongoing need for effective interventions to address chronic pain conditions such as residual limb pain, neuroma pain, and phantom limb pain, that remain prevalent and often debilitating challenges for individuals with amputation.

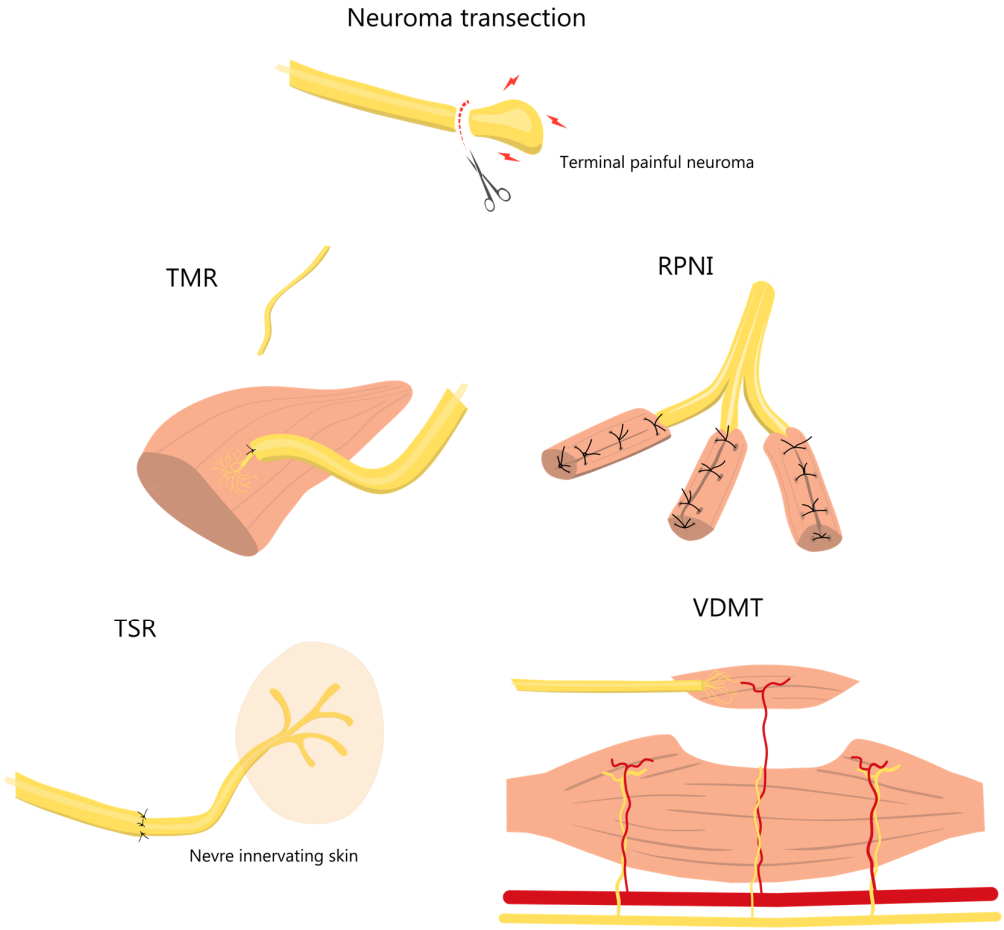

Figure 17. *Reconstructive surgical treatment strategies for terminal painful neuromas. Following neuroma transection, options include Targeted Muscle Reinnervation (TMR), Regenerative Peripheral Nerve Interface (RPNI), Targeted Sensory Reinnervation (TSR), and Vascularized Denervated Muscle Targets (VDMT).*

6.3 Barriers to Implementing Reconstruction Techniques in Clinical Practice

Despite evidence that proactive reconstruction techniques yield better outcomes than non-reconstructive approaches, their adoption in clinical practice remains limited worldwide. This gap arises from a combination of systemic, educational, and economic barriers. Foremost is the lack of high-quality, large-scale clinical data to definitively support routine use, which hinders broader acceptance[162–164]. Knowledge dissemination is also limited, as many surgeons are unfamiliar with modern nerve reconstruction methods or lack access to specialized training. Although all surgeons are technically authorized to operate on nerves, nerve specialists are rarely primarily involved in amputation-related pain management, resulting in missed opportunities to utilize new advancements.

Moreover, several structural factors can hinder the implementation of advanced surgical techniques in amputation procedures. One such factor is the assignment of amputation surgeries to less experienced surgeons, often during off-hours, which may reduce the likelihood of incorporating complex procedures like TMR or RPNI. Additionally, the low volume of amputation procedures in many hospitals limits both routine implementation and skill retention of these advanced techniques[165]. Financial disincentives, including a decline in insurance reimbursement for reconstructive procedures between 2014 and 2024[166], pose yet another barrier in some countries. Overcoming these challenges will require not only stronger clinical evidence but also enhanced training programs, interdisciplinary collaboration, and supportive health policies to facilitate the widespread adoption of reconstructive strategies in amputation care.

Evidence-Based Medicine

Evidence-based medicine (EBM) integrates high-quality clinical research, clinical expertise, and patient values to inform healthcare decisions. These three core pillars ensure that patient care is scientifically grounded, tailored to individual needs, and based on professional judgment[167]. Clinical studies form the foundation of EBM, and the type and design of a study largely determine the strength and reliability of the evidence it produces. Various frameworks and grading systems exist to assess the quality of evidence, often categorizing it into hierarchical levels. These levels typically range from systematic reviews and RCTs, which provide the highest quality evidence, to case reports and expert opinion, which are considered lower on the evidence spectrum (*Figure 18*).

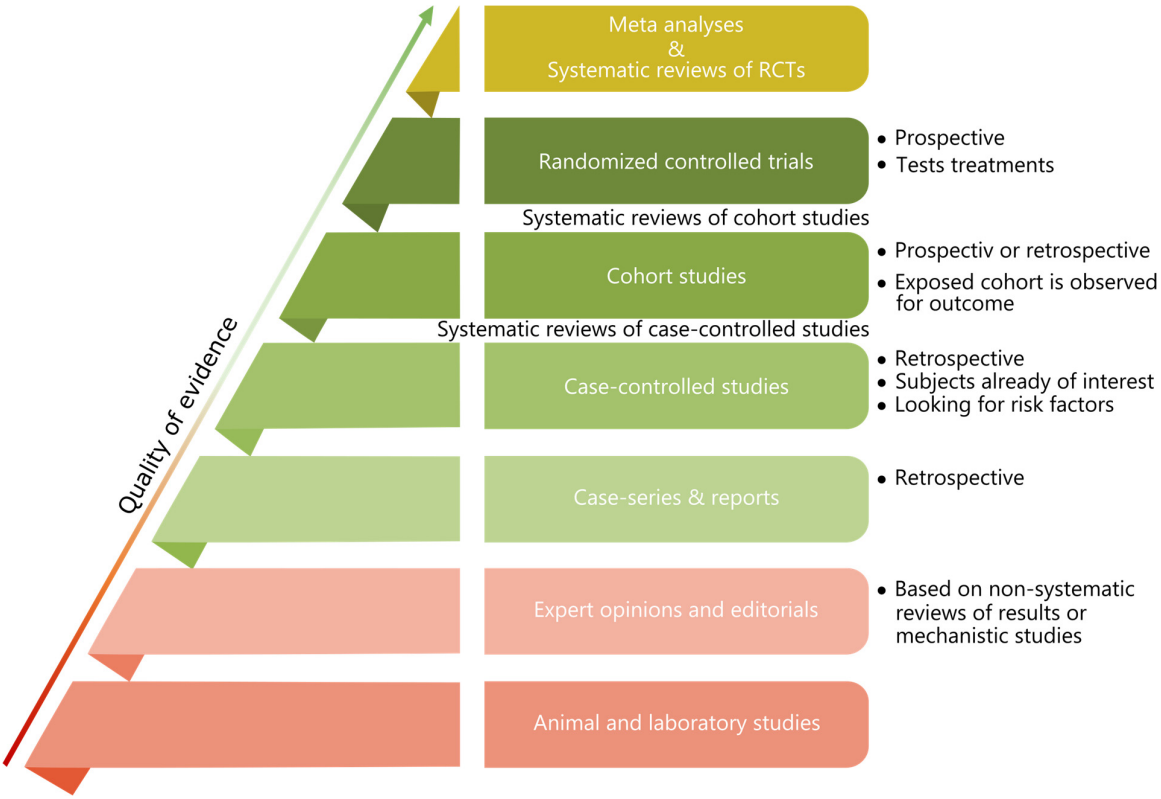

Figure 18. *Hierarchy of evidence in evidence-based medicine. The pyramid illustrates levels of clinical research evidence, with meta-analyses and systematic reviews of randomized controlled trials (RCTs) at the top, representing the highest quality of evidence. Each descending level reflects a lower strength of evidence, based on study design and methodological rigor. The categories range from prospective RCTs and observational studies (cohort and case-control), to retrospective reports, expert opinions, and preclinical research such as animal and laboratory studies, which provide foundational insights but are least generalizable to clinical practice.*

Lack of High-Quality Data for Proactive Reconstructive Surgical Treatments

Upon reviewing available research on the efficacy of TMR and RPNI for preventing and treating postamputation pain, we found that most studies fall in the lower tier of the evidence pyramid, where the quality is lower, and the risk of bias is higher (*Figure 19*). Furthermore, only one RCT is investigating TMR's treatment effect on chronic postamputation pain[31]. Notably, the study population in this RCT was limited to 28 patients. The authors initially aimed to recruit 200 patients; however, enrollment was halted after three years due to a slow recruitment pace[31]. Additionally, at the RPNI side of the evidence pyramid, no RCT has evaluated the effectiveness of RPNI surgery in either treating or preventing postamputation pain (*Figure 19*).

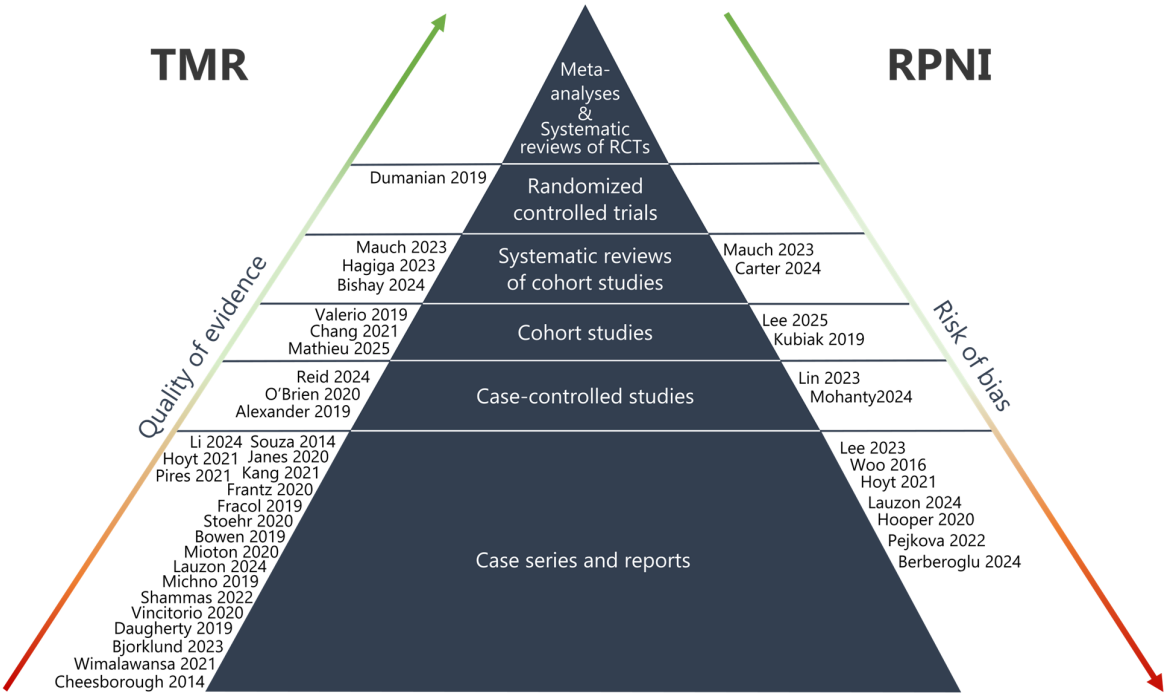

Figure 19. *Studies reporting the efficacy of Targeted Muscle Reinnervation (TMR)*[26, 31, 156–158, 162, 163, 168–189] *(to the left) and Regenerative Peripheral Nerve Interface (RPNI)*[32, 159, 162, 164, 172, 184, 190–196] *(to the right) for preventing and treating postamputation pain (last updated 2025-05-15). The studies are categorized by design, with those higher in the evidence pyramid offering greater quality and those lower carrying a higher risk of bias.*

Moreover, beyond the type of study design, several methodological limitations are consistently observed across the reviewed studies. These include, but are not limited to, small sample sizes, absence of prospective data collection, lack of control or comparison groups, and limited follow-up durations. In some cases, there is considerable variability in follow-up time within the same study, which can affect the consistency and reliability of outcome assessments. Additionally, heterogeneous study populations, a common challenge in amputation research, are present in several studies. Such variability in patient characteristics, including the cause of amputation, comorbidities, and level of limb loss, introduces potential confounding factors that complicate data interpretation. As a result, it becomes difficult to attribute observed effects solely to the intervention under investigation, thereby limiting the strength of the conclusions that can be drawn.

CHAPTER 7

Bridging the Knowledge Gap Through a Randomized Controlled Trial

To bridge the knowledge gap, we designed an international, multicenter, double-blinded randomized controlled trial comparing the efficacy of TMR and RPNI for the treatment of postamputation pain against each other and the intra-muscle transposition technique (*Paper III*[39]). To mitigate the challenges discussed in the previous chapter, such as low sample sizes and recruitment difficulties, we established collaborations with multiple hospitals across Europe, North and South America, and Australia.

7.1 Trial Objective and Design

We designed a multicenter, double-blind, prospective, superiority RCT that evaluates the effectiveness of three surgical approaches for treating postamputation pain in individuals with lower and upper extremity amputations. The primary objective is to compare the efficacy of nerve reconstruction techniques, specifically TMR and RPNI with an active control. The active control consists of implanting the severed nerves into a remnant muscle that retains its native innervation.

The RCT is conducted across nine hospitals in seven countries. 110 participants with major limb amputation will be recruited and randomly assigned to one of three surgical treatments, TMR, RPNI, or intra-muscle transposition, in equal groups (n = 37 per group). Follow-ups will be conducted at 1-, 3-, 6- and 12-month post-surgery and at 2- and 4-year post-surgery. After the 12-month follow-up, the study will be unblinded for both evaluators and participants. If a participant is dissatisfied with their treatment outcome, they may request an alternative procedure, with eligibility determined through medical evaluation and consultation with the clinical investigator. *Figure 20* presents the study flowchart.

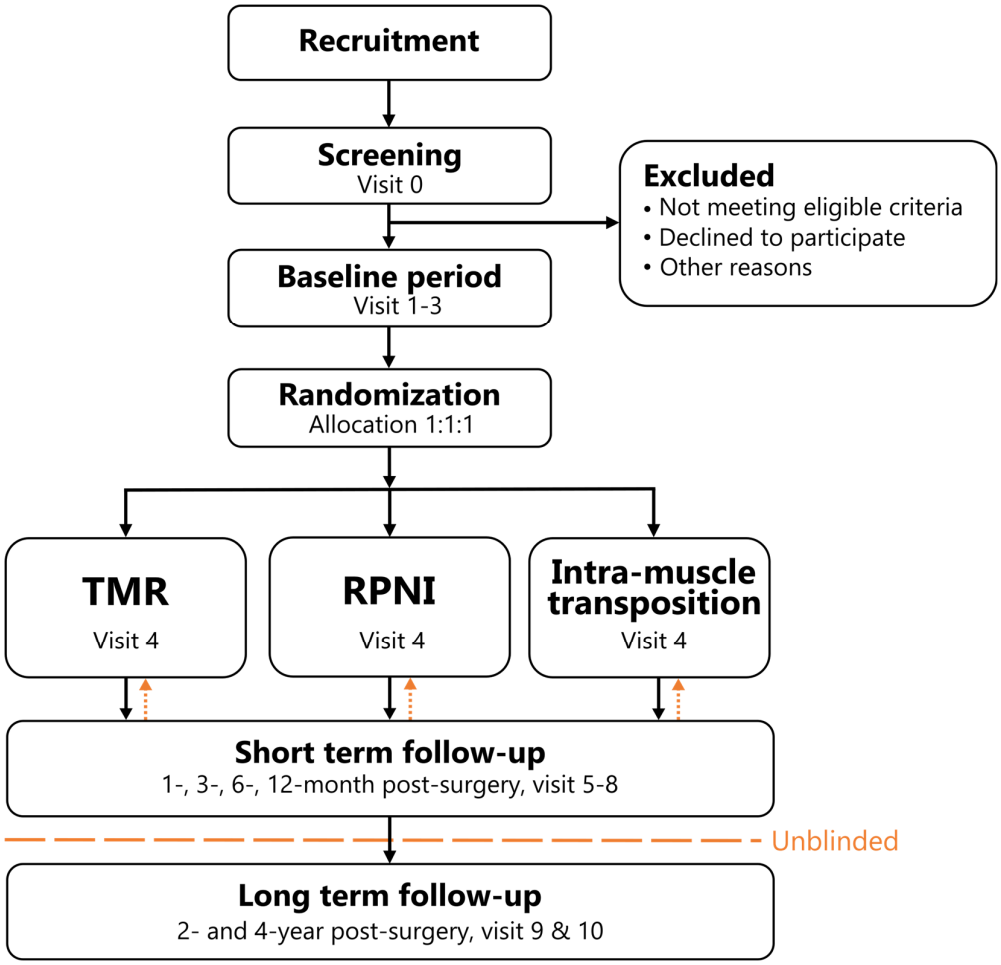

Figure 20. *Study flowchart of the randomized controlled trial (RCT). 110 participants with major limb amputations will be recruited and randomly assigned to one of the surgical treatments for postamputation pain in equal proportions. Follow-up assessments will be conducted both in the short term and long term. The study will be unblinded at 12 months post-surgery, allowing for a discussion of treatment outcomes with the clinical investigator at each site.*

Interventions

The interventions to be evaluated and compared in the trial are TMR, RPNI surgery, and standard treatment consisting of neuroma excision followed by intra-muscle transposition (*Figure 21*).

Targeted Muscle Reinnervation

TMR is a surgical technique in which a residual peripheral nerve is redirected to an available, denervated muscle within the residual limb (*Figure 21*, *upper*). The procedure consists of three key steps: preparation of the donor nerve, identification of a motor branch to the target muscle, and nerve coaptation. First, the donor nerve is prepared by identifying the nerve with a painful neuroma. The neuroma is then resected until healthy fascicles are exposed. Next, a motor branch to a nearby target muscle is identified, with muscle contraction confirmed using a handheld nerve stimulator. If multiple motor branches are present, the one producing the strongest contraction is selected. The motor branch to the target muscle is then transected as close as possible to its entry point, ideally within 1 cm, without causing tension, thereby temporarily denervating the muscle. In the final step, the previously resected nerve stump is transferred and coapted to the newly severed motor branch, which innervates the target muscle. This connection is secured using 2–3 non-resorbable monofilament sutures to ensure stability and facilitate nerve regeneration.

Regenerative Peripheral Nerve Interface

The RPNI procedure involves dividing the residual peripheral nerve into multiple fascicles, each implanted into a skeletal muscle graft (*Figure 21, middle*). The procedure begins with identification of the nerve containing a painful neuroma, followed by resection of the neuroma until healthy fascicles are exposed. A longitudinal intraneural dissection of approximately 2 cm is then performed to separate individual fascicles. Next, autologous muscle grafts are harvested from a healthy donor site, and each dissected nerve stump is placed centrally within a muscle graft, aligned parallel to the muscle fibers. The nerve stump is secured to the muscle graft proximally and distally using non-resorbable monofilament sutures. The muscle graft is then wrapped around the nerve stump and anchored with additional sutures at the base and along the walls of the folded graft, forming an RPNI. This process is repeated for each fascicle obtained from the transected nerve. Finally, the RPNIs are positioned in a protected area, ensuring they remain comfortably situated and free from weight-bearing surfaces of the limb.

Standard Procedure, Neuroma Excision Followed by Intra-muscle Transposition

The standard treatment involves transection of the terminal neuroma and implanting the nerve into an adjacent muscle (*Figure 21, bottom*). First, the surgeon identifies the affected nerve containing a painful neuroma and resects it up to the level of healthy fascicles. Next, a nearby muscle is selected, ensuring it is not involved in joint motion and has limited functional output for the nerve. The nerve is then carefully embedded at least 1 cm within the muscle without applying tension and secured with 1–2 non-resorbable monofilament sutures.

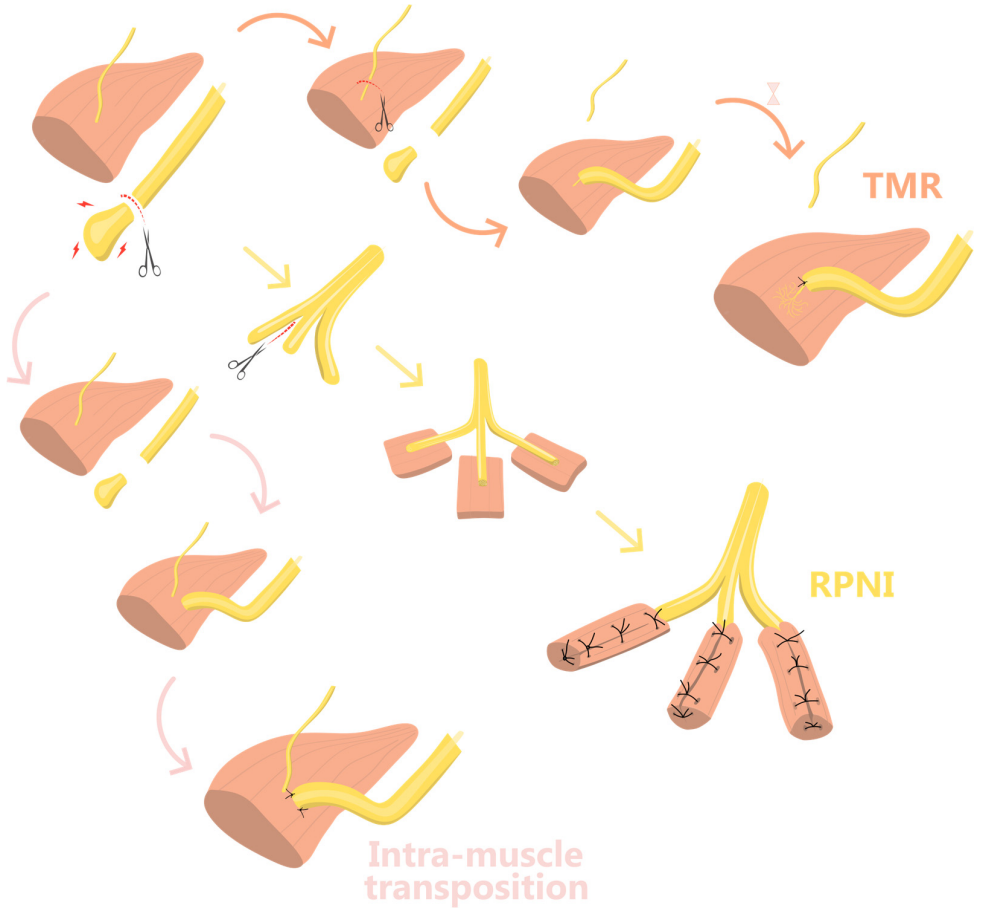

Figure 21. *Schematic representation of the three surgical approaches evaluated in the trial: Targeted Muscle Reinnervation (TMR), Regenerative Peripheral Nerve Interface (RPNI), and control treatment (intra-muscle transposition).*

Outcomes

Primary Outcome Measure

The primary outcome of this study is the mean change in residual limb pain intensity, assessed by the difference in Numerical Rating Scale (NRS, 0–10) scores between baseline (visits 0–3) and the 1-year postsurgical follow-up.

Secondary Outcome Measures

Secondary outcome measures include the mean change in neuroma pain and phantom limb pain intensity, assessed using NRS scores (0–10) from baseline (visits 0–3) to the 1-year follow-up. Additional secondary outcomes encompass pain frequency, duration, interference, and quality (*Table 2*), as well as factors that may influence variations in any type of pain, such as phantom sensations, telescoping, or motor ability, and changes in prosthetic use, or medication adjustments. Data in the RCT are collected by standardized questionnaires and study-specific questionnaires; for more details, see *Paper III*[39].

Table 2. *The study utilizes questionnaires categorized by pain type: residual limb pain (RLP), neuroma pain (NP), phantom limb pain (PLP), and general pain.*

Questionnaire	RLP	NP	PLP	General pain
Pain Survey				
• NRS (Numerical Rating Scale) Score[197]	X	X	X	
• Pain Frequency	X	X	X	
• Pain Rating Index (PRI)[197]	X	X	X	
• Pain Localization			X	
• Weighted Pain Distribution			X	
• Intrusion of Pain				X
Pain Disability Index (PDI)[198]				X
EuroQoL (EQ-5D-5L)[199]				X
Pain Self-Efficacy Questionnaire (PSEQ-2)[200, 201]				X
Pain Catastrophizing Scale-6 (PCS-6)[202]				X
Patients' Global Impression of Change (PGIC)				X
Expectations for Complementary and Alternative Medicine Treatments (EXPECT-SF)[203]				X

RLP, Residual Limb Pain; **NP**, Neuroma Pain; **PLP**, Phantom Limb Pain

Blinding

The study is structured as a double-blind trial, in which both the participant and the evaluator remain unaware of the surgical treatment received. All participants undergo identical study-specific assessments, regardless of their assigned surgical group. The only distinguishing feature is that individuals in the RPNI group will have an additional, inconspicuous scar at the muscle donor site, which is unlikely to reveal group allocation to the participant. Participants are informed that the trial compares three established surgical treatments, minimizing bias from expectations of superiority.

Blinding is maintained for both participants and evaluators for up to 12 months post-surgery, after which the study will be unblinded for both parties. Clinical investigators at each site, who are aware of the treatment assignments, are excluded from outcome analyses. Furthermore, all outcome data are formatted identically across groups, making it impossible to deduce treatment allocation without access to the key linking participants' codes to their assigned procedures.

Randomization

Participants will be assigned to one of the three treatment groups using a minimization-based allocation scheme, which optimally reduces imbalances across groups. Randomization will follow a 1:1:1 ratio, ensuring an equal distribution of major limb amputations among the groups. The allocation process will aim to minimize imbalances based on the following factors:

- Level of amputation (upper or lower limb)

- Baseline residual limb pain, categorized by the NRS score as medium (4–6) or high (7–10)
- Investigation site, including Sweden, Italy, Canada, Chile, Australia, the UK, and the USA

Participant randomization will be conducted using the REDCap randomization module[204]. Upon recruitment, eligible participants' minimization factors will be entered into the software, which will then assign them to a treatment group and automatically generate a pseudonym code.

7.2 Statistical Analysis

Sample Size Calculations

The sample size calculation is based on two previous studies investigating surgical treatments for RLP[31, 32], and the limited availability of eligible participants. To achieve a minimum power of 80% using Fisher's non-parametric permutation test, assuming a standard deviation for TMR and RPNI to be 2.2 and for the control group 3.3[31] with a mean difference of 2.0 and a significance level of 5% at a 2:1 allocation ratio (TMR and RPNI vs control), a minimum of 84 participants (n = 28 per group) is required. When comparing each reconstructive technique individually to the control group in a 1:1 ratio (TMR vs. control and RPNI vs. control), using the same assumptions, a total of 99 participants (n = 33 per group) is needed to maintain 80% power, assuming a mean difference of 2 NRS points and a 5% significance level. Considering an expected dropout rate of approximately 10%, the study aims to randomize a total of 110 participants to ensure sufficient statistical power.

Statistical Analysis Plan

The statistical analyses will be conducted through pairwise comparisons of the surgical techniques according to the following scheme:

1. Reconstructive techniques vs. control: TMR and RPNI compared to control (2:1)
2. Individual comparison of each reconstructive technique vs. control: TMR vs. control (1:1) and RPNI vs. control (1:1)
3. Comparison between reconstructive techniques: TMR vs. RPNI (1:1)

For the primary outcome, which measures the mean difference in the change of RLP (NRS score, 0–10) between baseline and the 1-year follow-up, an ANCOVA will be used to compare independent means in the intention-to-treat (ITT) population at a 5% significance level. This analysis will be adjusted for stratification (minimization) variables, including baseline NRS RLP score, level of amputation, and study site. Imputation will be performed using the last observation carried forward method. Additionally, a sensitivity analysis will be conducted using a two-sided non-parametric permutation test for independent means on the ITT population. A complementary analysis of the primary outcome will also be performed in the per-protocol (PP) population. The key results will include the mean difference with a 95% confidence interval, effect size, and p-value.

Secondary analyses will be conducted both unadjusted and adjusted for the ITT and PP populations. Unadjusted analyses will use Fisher's non-parametric permutation test for continuous variables, the Mantel–Haenszel chi-square test for ordered categorical variables, and Fisher's exact test for dichotomous variables. Adjusted analyses will involve ANCOVA for continuous variables and multivariable logistic regression for dichotomous variables.

Exploratory analyses will examine subgroup differences based on factors such as lower versus upper extremity amputation, right versus left extremity, sex, cause of amputation, baseline NRS pain score (categorized as medium: 4–6 or high: 7–10), time since amputation, and age. These analyses will first be conducted within each subgroup and then pooled for a comprehensive assessment. All statistical tests will be two-sided and conducted at a 5% significance level. For safety monitoring, an independent committee consisting of a medical expert and a statistician will review interim data once half of the study population has completed the 1-year follow-up.

CHAPTER 8

Standardizing Surgical Techniques

As the TMR and RPNI techniques have been globally adopted since their invention, variations in their execution have emerged. To address this, we collaborated with leading experts to establish a consensus on standardized procedural guidelines (*Papers IV*[40] and *V*[41]*)*. This effort had two primary goals. First, in our multicenter RCT, where multiple surgeons perform the procedures, standardization is essential to minimize bias. Second, we aim to facilitate broader adoption of these techniques among clinicians in amputation care.

Previous attempts to establish a consensus on the TMR technique have concluded without reaching clear agreement, highlighting ongoing variability in clinical practice and interpretation[205]. Therefore, the present work is particularly important, as it aims to provide structured guidance and contribute to greater standardization of both the TMR and RPNI techniques.

8.1 Standardization Process

The standardization process consisted of four main steps: 1) drafting a general protocol based on previously published literature, 2) reviewing the protocol through cadaveric dissection, 3) refining the protocol in a dedicated workshop, and 4) consulting expert surgeons outside the RCT.

First, we developed a surgical protocol using published literature and the expertise of Dr. Paolo Sassu, one of the clinical investigators involved in the trial design. This draft was then shared with all surgeons participating in the RCT, who were invited to attend an in-person workshop. The workshop was conducted in two parts: first, the drafted protocol was performed step-by-step in a cadaver, with any uncertainties or discussion points noted. In the second part, these points were thoroughly reviewed and debated. Based on these discussions, the protocol was revised and distributed to RCT surgeons who could not attend, as well as to external experts in the field. After gathering feedback from all experts, the protocol was finalized and shared with all individuals involved. Consensus was ultimately achieved through online communication.

During the standardization process, questions regarding specific aspects of the techniques were raised (*Table 3*). To the best of our knowledge, some of these questions, such as number 7, have never been discussed before among this large consortium of surgeons.

Table 3. *Questions and corresponding solutions/consensus discussed during the standardization process for each surgical procedure, categorized into: Targeted Muscle Reinnervation (TMR), Regenerative Peripheral Nerve Interface (RPNI), intra-muscle transposition (control), and general considerations applicable to all three procedures.*

	Question	Solution/Consensus
TMR	1. Should the target muscle be fully denervated from all nerves?	Denervate the target muscle completely when possible.
	2. If several innervation points are identified in the same muscle target, which innervation point should be used as the target?	Use the known proximal innervation points as the targets when possible.
	3. How far away from the innervation point should the coaptation be?	Aim for less than 1 cm.
	4. Which target muscle(s) should be used for the donor nerve?	See Table 1[40], suggesting which target muscle should be used for specific donor nerves at each amputation level.
	5. Where should the coaptation suture be placed?	In the center of the donor nerve.
	6. In scenarios where, for instance, painful neuromas are present in both the median and ulnar nerves at the transhumeral level, the biceps short-head muscle is recommended as the target for both nerves. If multiple innervation points are identified within the target muscle, can more than one nerve be coapted to different innervation points in the same target muscle?	If multiple innervation points are identified within the same target muscle, two donor nerves can be coapted to different innervation points within the same target muscle. While this may not be suitable for prosthetic control, it could be beneficial for pain management.
	7. How should the coaptation step be performed, nerve-to-nerve coaptation with either short or long recipient nerve, or nerve-to-neuromuscular entry zone?	Nerve-to-nerve coaptation with a maximum 1 cm of the recipient nerve.
	8. What to do with the nerve stump that has been denervated?	Move away from the coaptation site without any specific management.
RPNI	9. Should the nerve end be sutured into the muscle graft or remain free?	Do not suture the nerve end into the muscle graft, the transected portion of the nerve remains free.
	10. What dimensions should be used for the muscle graft?	3 cm (length) × 1.5 cm (width) × 0.5 cm (thickness).
	11. Should all muscle grafts be harvested at the same time or after each RPNI construction?	Perform all muscle grafting at the same time, thereafter, do all the RPNI constructs at once.
	12. How many fascicles per nerve per level of amputation?	See Table 1[41], suggesting the number of neural fascicles that should be prepared for each nerve depending on the level of amputation.
Intra-muscle transposition	13. How far in the muscle should the nerve stump be placed?	Minimum 1 cm inside the muscle.
	14. How should the transposed nerve stump be secured in the muscle?	Suture the epimysium to the epineurium with 1-2 sutures.
General for all procedures	15. Do the neuroma need to be isolated?	Isolation of the neuroma is optional.
	16. Do the neuroma need to be resected?	Resection of the neuroma is optional when challenging.
	17. Usage of nerve glue?	No use of nerve glue.

TMR, Targeted Muscle Reinnervation; **RPNI**, Regenerative Peripheral Nerve Interface

8.2 Facilitating the Dissemination of Surgical Techniques

The second objective of standardizing the protocols was to create an open-access tool aimed at empowering clinicians worldwide to effectively implement TMR and RPNI and bring their benefits to their patients. To ensure ease of use and widespread accessibility, the protocols are accompanied by video demonstrations (*Figure 22*), where each step are carefully recorded either in the operating room during live procedure or on a cadaver model to illustrate the technique. These are complemented by clear, step-by-step written instructions and detailed illustrations (TMR, *Figure 23*; RPNI, *Figure 24*). This multi-modal approach potentially ensures that clinicians, regardless of their level of experience, can easily follow the protocols and confidently perform the procedures.

Figure 22. *Video recordings of the surgical techniques used in the randomized controlled trial. Left and center: recording of the Targeted Muscle Reinnervation (TMR) procedure in the operating theater. Right: recording of the Regenerative Peripheral Nerve Interface (RPNI) technique in the cadaver lab.*

To further support clinical implementation, the protocols not only provide step-by-step guidance but also include detailed recommendations, highlight critical steps, and address potential troubleshooting scenarios. For instance, the TMR protocol contains a table recommending specific target muscles for each donor nerve at various amputation levels. Similarly, the RPNI protocol outlines the optimal number of neural fascicles to include per nerve, depending on the level of amputation. Furthermore, achieving successful outcomes with TMR relies heavily on several key procedural steps. One of the most crucial is adequate mobilization of the donor nerve stump to ensure tension-free nerve coaptation. Other essential elements include complete denervation of the target muscle and the selection of known proximal motor entry points as ideal coaptation sites.

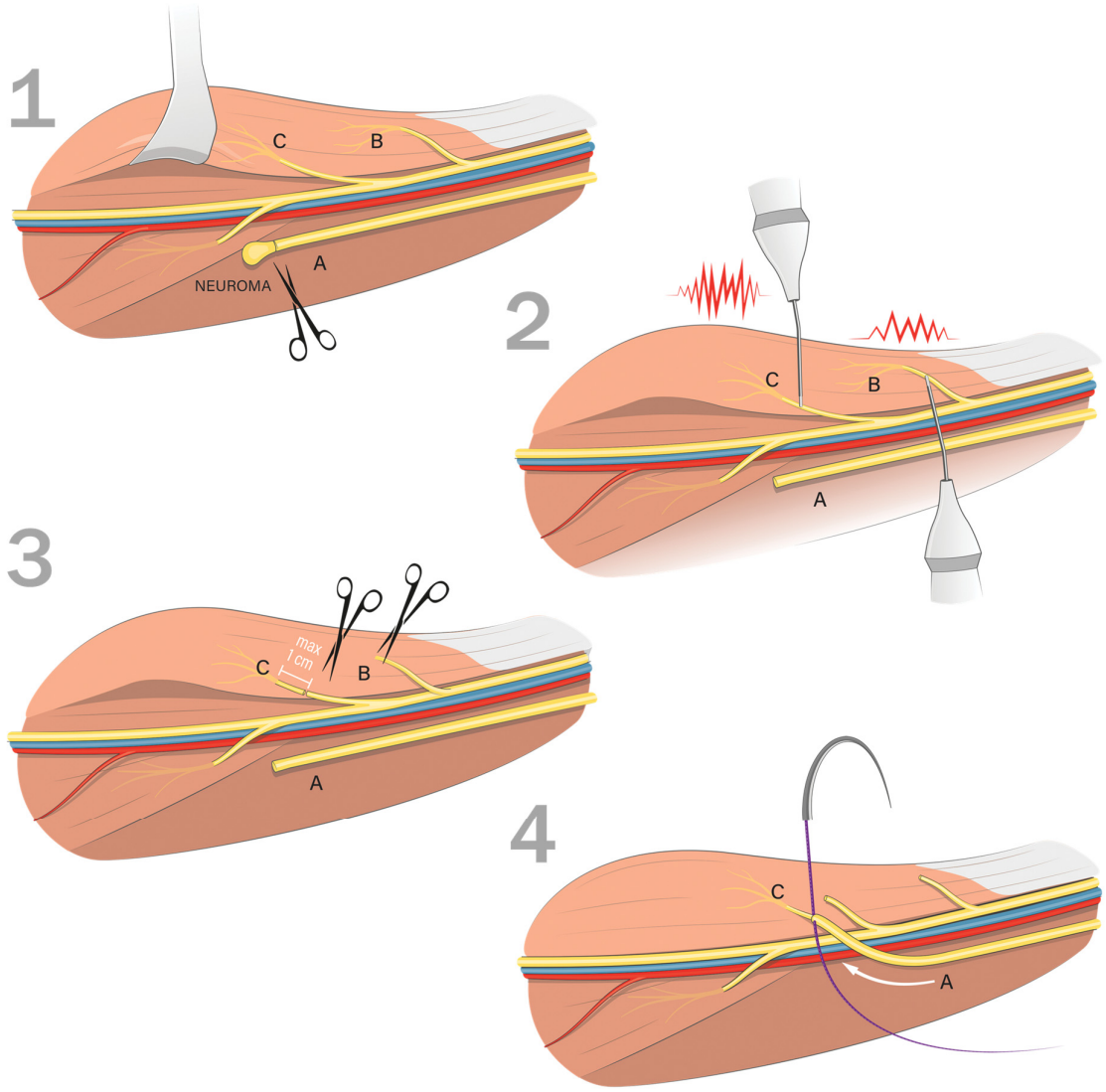

***Figure 23**. Flowchart of the Targeted Muscle Reinnervation (TMR) technique. (1) Identify and isolate the donor nerve with the painful neuroma (A), mobilize the nerve, and transect the neuroma back to healthy neural fascicles. (2) Identify motor nerve(s) to the target muscle and confirm muscle contraction using a handheld nerve stimulator. (3) Select the motor branch that produces the largest contraction (C), transect it without tension (max 1 cm), and denervate other motor branches if possible (B). (4) Suture the donor nerve to the recipient nerve, placing the stitch at the center of the donor nerve, and reinforce with two to three microsutures, securing the donor nerve's epineurium to the recipient's fascia and epimysium. The illustration originates from Paper IV*[40].

In RPNI surgery, proper muscle graft harvesting is essential. The muscle should be dissected along its fiber axis, with all connective tissue removed to optimize regeneration. The choice of harvest site depends on muscle availability. The size ratio between the nerve stump and muscle graft is crucial. Thick grafts risk central necrosis, while undersized or insufficiently denervated grafts may lead to neuroma formation. For a muscle graft measuring 3 cm × 1.5 cm × 0.5 cm, the nerve stump should be no larger than 4–6 mm in diameter. For larger nerves (up to 10 mm in diameter), graft width can be increased to 2 cm, as long as it fully covers the nerve and extends at least 1 cm proximally, ensuring tension-free coaptation and adequate revascularization. For thick nerves, like the sciatic nerve, fascicular dissection is recommended to create multiple smaller RPNIs rather than a single large one (see Table 1[41]), for improving reinnervation and reducing necrosis risks.

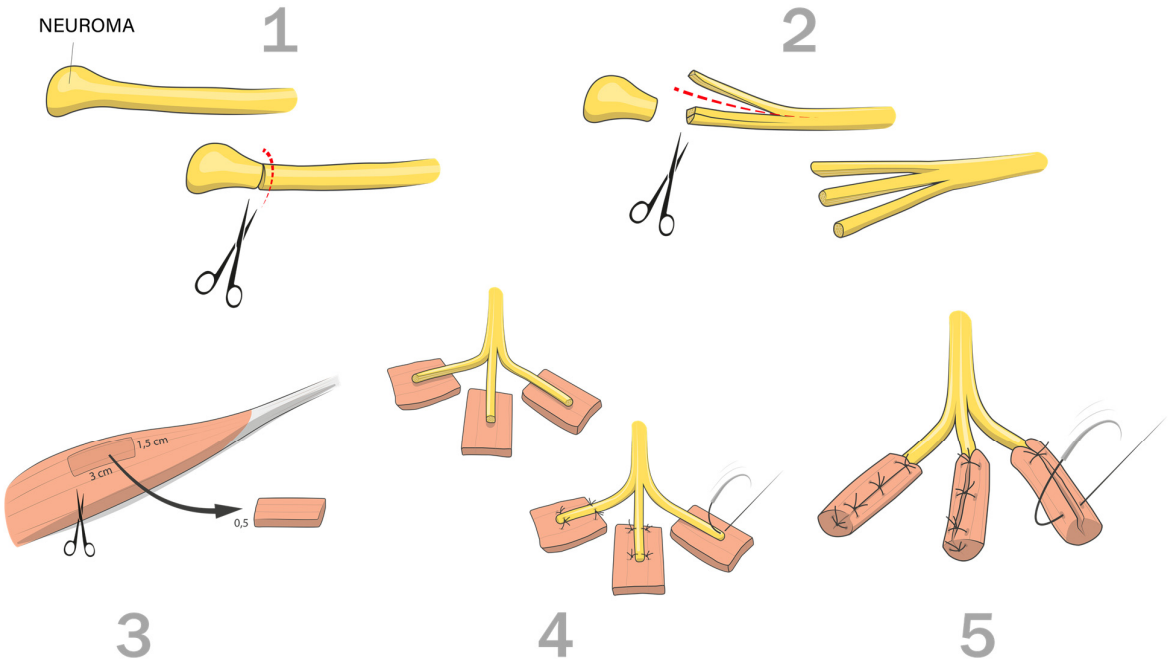

Figure 24. *Schematic illustration of the Regenerative Peripheral Nerve Interface (RPNI) procedure. (1) Identify and isolate the nerve with the painful neuroma, mobilize it, and transect the neuroma back to healthy neural fascicles. (2) Perform longitudinal intraneural dissections from the distal end of the nerve, with the number of fascicles determined by the amputation level and nerve size. (3) Harvest a healthy native muscle graft (3 cm × 1.5 cm × 0.5 cm). (4) Insert the nerve fascicle into the center of the muscle graft, ensuring alignment parallel to the muscle fibers, and secure with sutures at both ends of the nerve stump. (5) Fold the muscle graft around the nerve fascicle and secure it in place. The illustration originates from Paper V*[41].

CHAPTER 9

Summary of Thesis Contributions

This thesis contributes to the advancement and clinical adoption of surgical innovations addressing functional and pain-related challenges in individuals with amputation. It introduces a novel stimulation concept for enhancing osseointegration using existing hardware within a known safety range. Furthermore, it demonstrates that this stimulation paradigm positively impacts bone cell processes essential for osseointegration, including cell survival and soluble collagen production.

Prior to this thesis, no study had directly compared the TMR and RPNI procedures to each other or to a standard technique in evaluating their effectiveness for treating postamputation pain. This thesis has contributed to the initiation of an international, multicenter, double-blind RCT with the primary goal of providing high-quality evidence of the superiority of the TMR and RPNI techniques. As part of the RCT work, these procedures were standardized through a consensus among participating surgeons and leading experts in each technique, resulting in written guidelines and instructional video recordings. This work plays an important role in disseminating the TMR and RPNI procedures, supporting their widespread clinical adoption, and aiding clinicians in incorporating these techniques into amputation management.

This chapter offers an overview of the papers that form the foundation of this thesis. The complete versions of these papers are found in Part II.

Paper I

Pettersen E, Anderson J, Ortiz-Catalan M.

Electrical stimulation to promote osseointegration of bone anchoring implants: a topical review. *J Neuroeng Rehabil.* 2022 Mar 21;19(1):31.

doi: 10.1186/s12984-022-01005-7. PMID: 35313892; PMCID: PMC8939223.

Bone-anchored implants offer a superior alternative to traditional socket prostheses but are hindered by extended healing times and in some cases suboptimal bone-implant interfaces. Electrical stimulation shows promise in promoting osseointegration. This review examines scientific evidence on electrical stimulation, focusing on studies using titanium implants as stimulating electrodes. A literature search was conducted in PubMed, Google Scholar, and the Chalmers University of Technology Library, identifying 55 relevant publications. After screening, 13 studies were selected for analysis. Most studies reported benefits of electrical stimulation in processes influencing osseointegration, supporting its potential use. However, conclusive evidence in humans remains lacking. Additionally, optimal stimulation parameters have not been sufficiently explored, highlighting a key gap for clinical application. Establishing standardized reporting methods is crucial to enabling meta-analysis and evidence-based treatments.

The author of this thesis collected and analyzed the data, drafted and revised the manuscript. JA and MOC supervised the research and revised the manuscript.

Paper II

Pettersen E, Shah FA, Ortiz-Catalan M.

Enhancing osteoblast survival through pulsed electrical stimulation and implications for osseointegration. *Sci Rep*. 2021 Nov 17;11(1):22416.

doi: 10.1038/s41598-021-01901-3. PMID: 34789829; PMCID: PMC8599699.

In this study, we developed a novel method for delivering electrical stimulation to titanium implants using parameters previously tested in peripheral nerve stimulation. We established an *in vitro* model with Ti6Al4V implants pre-cultured with MC3T3-E1 preosteoblasts and subjected them to electrical stimulation for 72 hours at varying pulse amplitudes (10 µA and 20 µA) and frequencies (50 Hz and 100 Hz). Our results indicate that asymmetric charge-balanced pulsed electrical stimulation enhances cell survival and collagen production in a dose-dependent manner. These findings suggest that this form of stimulation, mimicking peripheral nerve stimulation, may improve peri-implant bone healing, particularly in regions where implanted electrodes are readily accessible, such as neuromusculoskeletal interfaces. Potential applications include accelerating healing, restoring early function, and promoting the re-osseointegration of failing bone-anchored implants.

The author of this thesis contributed to the study design, performed the experiments, collected and analyzed the data, and drafted and revised the manuscript. FA contributed to the study design, collected and analyzed the data, and drafted and revised the manuscript. MOC contributed to the study design and edited the manuscript.

Paper III

Pettersen E, Sassu P, Reinholdt C, Dahm P, Rolfson O, Björkman A, Innocenti M, Pedrini FA, Breyer JM, Roche A, Hart A, Harrington L, Ladak A, Power H, Hebert J, Ortiz-Catalan M.

Surgical treatments for postamputation pain: study protocol for an international, double-blind, randomised controlled trial. *Trials*. 2023 May 2;24(1):304. Erratum in: *Trials*. 2023 Oct 9;24(1):654.

doi: 10.1186/s13063-023-07286-0. PMID: 37131180; PMCID: PMC10155377.

There is a lack of high-quality evidence supporting surgical treatments for postamputation pain. To bridge this knowledge gap, we designed a study protocol for a multicenter, international, double-blind RCT evaluating two contemporary techniques, TMR and RPNI, against each other and compared to the standard of care for treating postamputation pain in individuals with major limb amputations. The primary objective of this RCT is to assess the effectiveness of these surgical techniques in treating postamputation pain. The primary outcome measure is the change in the numerical rating scale (NRS, 0–10) score between baseline to the one-year follow-up after surgery. The trial is being conducted across nine centers in seven countries. A total of 110 participants with major limb amputation will be recruited and randomly assigned to one of the three surgical treatments. Study participants are monitored through six follow-up visits during a four-year period after the intervention.

The thesis author designed the study, drafted and revised the manuscript. PS and MOC designed the study and revised the manuscript. All authors gave feedback on the study design and edited the manuscript.

Paper IV

Pettersen E, Sassu P, Pedrini FA, Granberg H, Reinholdt C, Breyer JM, Roche A, Hart A, Ladak A, Power HA, Leung M, Lo M, Valerio I, Eberlin KR, Kung TA, Cederna P, Souza JM, Aszmann O, Ko J, Dumanian GA, Ortiz-Catalan M.

Targeted Muscle Reinnervation: Surgical Protocol for a Randomized Controlled Trial in Postamputation Pain. *J Vis Exp*. 2024 Mar 8;(205).

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The growing global adoption of TMR has led to variations in the procedure. This article presents a comprehensive step-by-step protocol for performing TMR surgery and serves as the surgical protocol used in the RCT (ClinicalTrials.gov, NCT05009394). This protocol represents a consensus among a group of leading surgeons actively performing this technique. TMR is a surgical procedure that redirects nerves through a formal nerve transfer process, specifically targeting motor nerves and their associated motor end plates in the residual limb. The procedure consists of three main steps: preparation of the donor nerve, motor point identification, and nerve-to-nerve coaptation. In addition to the detailed step-by-step instructions, this article highlights critical steps, modifications, troubleshooting strategies, and the limitations of the technique while contextualizing its significance relative to existing methods. The protocol is published as a traditional written guide with descriptive illustrations, but more importantly, it includes an explanatory video detailing each step of the procedure. By providing these resources, we aim to facilitate the dissemination of the technique and make it more accessible to surgeons interested in incorporating TMR into amputation management.

The thesis author contributed to the step-by-step protocol, collected the data for representative results, drafted and revised the manuscript, and prepared the manuscript for the video recording. PS and FAP contributed to the step-by-step protocol. PS and MOC revised the manuscript and prepared the manuscript for the video recording. All authors gave feedback on the step-by-step protocol and edited the manuscript.

Paper V

Pettersen E, Sassu P, Pedrini FA, Granberg H, Reinholdt C, Breyer JM, Roche A, Hart A, Ladak A, Power HA, Leung M, Lo M, Valerio I, Eberlin KR, Ko J, Dumanian GA, Kung TA, Cederna P, Ortiz-Catalan M.

Regenerative Peripheral Nerve Interface: Surgical Protocol for a Randomized Controlled Trial in Postamputation Pain. *J Vis Exp*. 2024 Mar 15;(205).

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Here we present a step-by-step protocol for performing RPNI surgery, based on a global consensus among leading surgeons. The protocol serves as the standardized procedure used in the surgical RCT (ClinicalTrials.gov, NCT05009394). RPNI surgery involves removing the painful neuroma, longitudinally dissecting the donor nerve stump into fascicle groupings, and directly implanting these fascicles into free denervated skeletal muscle grafts. In addition to the detailed guide, the article discusses critical steps, adaptations, troubleshooting strategies, limitations, and the technique's comparative significance to established methods. The protocol is disseminated through traditional publication channels, including a written guide with explanatory illustrations, as well as a video demonstration. Our goal is to increase accessibility to this technique, helping surgeons interested in integrating it into their amputation management practices.

The author of the thesis contributed to the step-by-step protocol, collected the data for representative results, drafted and revised the manuscript, and prepared the manuscript for the video recording. PS and FAP contributed to the step-by-step protocol. PS and MOC revised the manuscript and prepared the manuscript for the video recording. All authors gave feedback on the step-by-step protocol and edited the manuscript.

CHAPTER 10

Concluding Remarks and Future Work

This thesis aimed to investigate and support the clinical adoption of innovative surgical techniques for individuals with major limb amputation, particularly those aimed at improving functional outcomes and addressing pain-related challenges. While significant progress has been made in developing advanced surgical methods for prosthetic attachment, motor control, sensory feedback, and the prevention and treatment of postamputation pain, these approaches have not yet been widely implemented in clinical practice. Even at major, well-respected hospitals, surgical techniques with the potential to greatly improve the quality of life for people with limb loss are not consistently incorporated into amputation management protocols.

Despite the clear potential of advanced surgical techniques to improve outcomes for individuals with limb loss, amputation surgery remains underprioritized and undervalued within the healthcare system. This is paradoxical, considering that amputation care represents a substantial economic burden. In the United States, for example, the lifetime healthcare cost for a person with a major limb amputation can exceed $500,000 to $1 million[206–208], with expenses stemming from repeated hospitalizations, prosthetic replacements, chronic pain management, and rehabilitation. Yet, the initial surgical procedure, which has profound implications for long-term pain, prosthetic function, and quality of life, often receives little attention or innovation. The way an amputation is performed significantly affects whether a person will experience debilitating phantom or residual limb pain, and whether they can use a prosthesis effectively. These are lifelong consequences that affect autonomy, employment, mental health, and overall well-being. For individuals who have lost a limb, the minimum standard of care should be an updated surgical approach, and a prosthetic rehabilitation plan tailored to their needs. Young patients, in particular, deserve access to the best available treatment, just as it would be unthinkable to deny a child a cochlear implant when medically indicated. It is time that amputation surgery and prosthetic rehabilitation are treated with the same urgency, precision, and investment as other life-altering interventions.

This thesis contributes to bridging the gap between emerging surgical innovations and their clinical implementation by presenting both foundational research and translational initiatives. One line of investigation assessed the potential of using electrical stimulation resembling peripheral nerve stimulation, commonly used for sensory feedback in prosthetic applications, to promote osseointegration in bone-anchored implants. Preliminary *in vitro* findings demonstrated that pulsed electrical stimulation, applied using clinically relevant parameters, can modulate cellular mechanisms associated with bone integration, supporting its potential therapeutic role in enhancing implant fixation or recovery following implant failure. In parallel, a multicenter RCT was initiated to generate high-quality evidence for the use of TMR and RPNI in the management of postamputation neuroma-related pain. Furthermore, a significant output of this thesis was the development of standardized, step-by-step surgical protocols, complemented by detailed written instructions, anatomical illustrations, and explanatory videos, to support the consistent global adoption of these procedures. Collectively, these contributions aim to advance the scientific foundation and clinical dissemination of modern amputation care strategies, ultimately improving long-term outcomes for individuals with limb loss.

The promising results presented in this thesis also point to several important directions for future research and clinical development. One key area is the optimization of stimulation parameters for pulsed electrical stimulation used in promoting osseointegration. Further studies should aim to refine variables such as pulse amplitude, frequency, and duration, while also considering both invasive and non-invasive electrode systems to increase the clinical applicability of this technique. Another critical aspect is infection control, as infection continues to pose a major risk in osseointegrated implants, hindering their wider adoption. Future investigations should examine whether electrical stimulation may also play a role in mitigating bacterial colonization, thereby supporting implant longevity.

In addition, successful integration of advanced surgical techniques into routine care depends on structured education. These innovations must become part of standard surgical training, equipping orthopedic surgeons, rehabilitation professionals, and related specialists with the knowledge and skills to implement them effectively. Finally, translating these methods into clinical practice will require systematic efforts to disseminate the standardized protocols developed in this thesis. This includes establishing training frameworks, certification pathways, and institutional strategies to facilitate broad, consistent application of reconstructive approaches in amputation care.

Beyond the clinical implementation of currently established techniques such as TMR and RPNI, the future of surgical innovation in amputation care lies in the development and translation of next-generation neural interface strategies. These emerging techniques, some currently explored in animal models, seek to establish more advanced bi-directional interfaces that can simultaneously enhance motor control and restore more naturalistic, intuitive sensory feedback. In contrast to current approaches, which are limited in the number of available control channels and often produce artificial or cognitively demanding sensory experiences, these novel interfaces aim to recreate the nuanced and embodied experience of natural limb function using biological constructs.

To enable clinical use of these surgically created sensorimotor interfaces, further development of closed-loop electronic systems is essential. These systems must support both neural recording for motor intent and targeted stimulation for sensory feedback, while offering higher channel counts, increased nerve activation specificity, and reliable wireless communication between the prosthesis and the human body. Achieving this level of integration will require interdisciplinary collaboration across neural engineering, regenerative medicine, and bioelectronics, as well as rigorous clinical trials to establish safety and efficacy. If successful, these innovations could represent a paradigm shift in neural reconstruction, offering patients more seamless integration with assistive technologies and, ultimately, restoring a greater sense of agency, function, and quality of life.

Importantly, the potential applications of these interface strategies extend beyond the amputation population. Similar concepts could be adapted for other neurological or peripheral disorders, such as spinal cord injuries, brachial plexus injuries, or peripheral neuropathies. In these contexts, the core principles of targeted nerve regeneration, signal amplification, and neural integration could be leveraged to re-establish volitional control, alleviate neuropathic pain, or restore functional connectivity across disrupted neural pathways. These cross-disciplinary applications not only expand the impact of this field but also open valuable opportunities for translational synergy and shared innovation across diverse domains of neurorehabilitation.

In conclusion, the research presented in this thesis contributes foundational knowledge, practical tools, and translational initiatives that help move modern amputation surgery from concept to widely adopted clinical reality. By supporting both scientific advancement and surgical dissemination, this work aims to improve long-term outcomes and quality of life for individuals with limb loss. As the field moves toward increasingly integrated neural-prosthetic systems, continued interdisciplinary collaboration and systematic clinical implementation will be essential to realize the full potential of these innovations.

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