Electrical Stimulation-Based Sensory Feedback in Phantom Limb Pain Treatment

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PhD Thesis by

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Preface

The research presented in this Ph.D. thesis was carried out at the center for Sensory Motor Interaction (SMI) in the Department of Health Science and Technology of Aalborg University between 2008 and 2011. This research was financially supported by the EU-funded 'TIME' project: Transverse Intrafasicular Multichannel Electrode System, grant no. CP-FP-INFSO 224012. Completion of this thesis would not have been possible without the support of both the SMI and TIME project team.

I would like to express my sincere thanks to my supervisor, Winnie Jensen, who supported and encouraged me throughout my Ph.D. work. She gave me a chance to pursue a research topic that was new for me and provided guidance and constructive feedback. I also want to extend my thanks to Ken Yoshida for his many valuable contributions to my work. I have indeed benefited from close collaboration with him.

I would also like to thank my colleagues, who have significantly contributed to the research presented in this thesis. I would especially like to thank Laura Petrini for providing advice on psychophysical methods, Line Lindhardt Egsgaard for her help with the EEG data analysis, and Knud Larsen for his assistance in solving technical problems in the software development. Lastly, I thank all the members of the NPI lab for participating in discussions on all aspects of this research, which helped shape my view on what research really is.

Special thanks go to my husband Ming for his patience and endless support and to my parents and brother, who always support me. The thesis is dedicated to our lovely daughter, Joyce, whose arrival added so much delight to my Ph.D. life.

English summary

Following amputation, up to 80% of amputees perceive pain in the missing part of the arm or leg, known as phantom limb pain (PLP). PLP can be extremely intractable, and there are no effective, long-lasting treatments currently available. Reorganization in the primary sensorimotor cortex has been found to be closely associated with PLP. Therefore, an approach targeting reversal of cortical reorganization may hold promise for PLP relief. The present thesis hypothesizes that providing sensory feedback through electrocutaneous stimulation of the residual limb may reverse cortical reorganization and consequently suppress PLP.

To address the hypothesis, five studies were conducted. Studies 1 and 2 examined the impact of stimulation parameters on the perception threshold and the evoked sensation, respectively. The stimulation location and pulse number were found to significantly affect the magnitude and quality of the perceived sensation. These two parameters were then considered to be able to effectively convey sensory information. Study 3 investigated human ability in sensory discrimination of the two identified parameters, in which satisfactory performance was obtained with able-bodied subjects. Based on the findings of the first three studies, the hypothesis was tested in study 4. An upper-limb amputee was trained in sensory identification to evaluate the effects on PLP and cortical reorganization. The results showed no changes in PLP and cortical reorganization, although the volunteer's identification accuracy improved over the course of the training period. As part of the EU-funded project 'TIME', a computerized tool was developed for evaluation of sensory feedback in a multi-channel intrafascicular stimulation system in study 5. This tool was used to assist in identifying optimal stimulation patterns that can evoke natural sensory feedback referred to the phantom limb. Sensory feedback using direct nerve stimulation may be an alternative treatment for PLP awaiting further clinical evaluation in future work.

Dansk resume

Efter amputation føler op til 80% af de amputerede personer smerter i den manglende del af armen eller benet; dette kaldes også fantomsmerter. Fantomsmerter kan være ekstremt voldsomme og der findes ingen effektive, langvarige behandlingsmetoder mod disse smerter. Reorganisering i primær sensorisk-motorisk cortex har vist sig at være tæt forbundet med fantomsmerter. Derfor kan en metode, der er rettet imod ændring af den kortikale reorganisation vise sig at være lovende i behandlingen af fantomsmerter. Denne afhandling antager som udgangspunkt, at frembringelse af sensorisk feedback gennem elektrokutan stimulation af det resterende lem kan ændre den kortikale reorganisering og som følge heraf dæmpe fantomsmerterne.

For at underbygge denne hypotese blev der udført fem studier. Studie 1 og 2 undersøgte effekten af stimulationsparametre på henholdsvis perceptionstærsklen og den fremkaldte fornemmelse. Det blev fundet, at stimulationssted og antallet af impulser væsentligt påvirker den opfattede fornemmelses styrke og kvalitet. De to parametre blev herefter bestemt til effektivt at kunne viderebringe sensoriske informationer. Studie 3 undersøgte menneskets evne til sensorisk diskrimination af de to identificerede parametre, hvor tilfredsstillende resultater blev opnået med raske forsøgspersoner. Baseret på resultaterne af de tre første studier blev hypotesen undersøgt i studie 4. Træning af sensorisk identifikation blev undersøgt hos en person med amputation i overekstremiteten for at undersøge effekten på fantomsmerter og kortikal reorganisering. Resultaterne viste ingen ændringer i hverken fantomsmerter eller kortikal reorganisering, selvom identifikationsevnen forbedredes i træningsperioden. Som en del af det EU-finansierede projekt 'TIME' blev der i studie 5 udviklet et computerværktøj til vurdering af sensorisk feedback i et multi-kanal intrafascikulært stimulationssystem. Dette blev anvendt til hjælp til identifikation af optimale stimulationsmønstre, som kan fremkalde naturlig sensorisk feedback, som refereres til fantomlemmet. Sensorisk feedback ved hjælp af direkte nervestimulation kan være en alternativ behandling for fantomsmerter, hvilket dog afventer nærmere fremtidig klinisk vurdering.

1. Background

Surgical limb amputations are typically due to peripheral vascular diseases, cancer, or diabetes (Nikolajsen and Jensen, 2001). Motor vehicle accidents, wartime conflicts, terrorist attacks and landmine explosions can also necessitate traumatic limb amputation in otherwise healthy people (Lacoux et al., 2002). In the USA, limb loss affects nearly 1.6 million individuals (Ephraim et al., 2005), and a recent study estimated that the number of people living with a limb loss will more than double by the year 2050 (Ziegler-Graham et al., 2008).

1.1 Non-painful phantom sensation

Virtually all amputees experience non-painful phantom sensations, i.e., the feeling that the removed limb still exists. The qualities of the phantom sensations include specific somatosensory experiences such as touch, cold, warmth, itching and other paraesthesias (Kooijman et al., 2000). In addition, patients often claim they can perceive kinesthetic features, such as the size, shape, and position of the missing limb, and even voluntary movements of the phantom limb, e.g., reaching out to grab an object, making a fist or moving their fingers individually (Weinstein, 1998). Involuntary phantom movements are also common, e.g., suddenly moving to occupy a new posture or suddenly developing a clenching spasm of the fingers (Ramachandran and Hirstein, 1998).

Phantom sensations may be evoked by applying stimulation on the ipsilateral face or the stump (Figure 1). These phantom sensations, usually called referred sensations, i.e., sensations perceived as originating from a body site other than the one stimulated, have been described frequently following amputation (Ramachandran and Hirstein, 1998; Grüsser et al., 2001; Ramachandran et al., 1995).

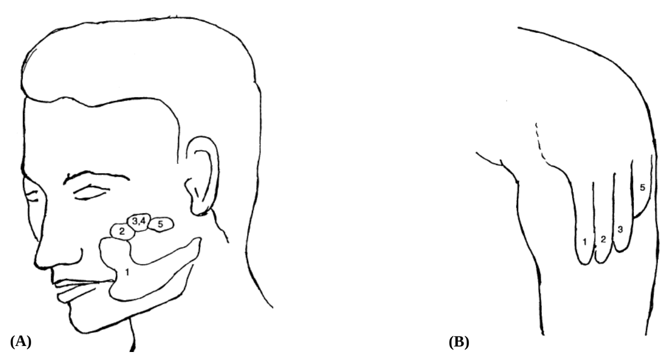

Figure 1. The distribution of referred phantom sensation in patient D. S., whose left arm was amputated 6 cm above the elbow joint due to injuries from a car accident. (A) Topographic arrangement of digits of the phantom hand on the ipsilateral face 6 months after amputation. (B) Topographic mapping of phantom digits in the region of the deltoid muscle on the stump (from Ramachandran et al. 1998).

1.2 Phantom limb pain (PLP)

1.2.1 Characteristics

In 50–85% of all amputees, pain develops in the limb that no longer exists (Weeks et al., 2010). This pain is termed phantom limb pain (PLP). PLP appears to be more common following a traumatic limb loss or if pre-amputation pain existed than after a planned surgical amputation of a non-painful limb (Ramachandran and Hirstein, 1998). PLP is more prevalent in adults than in children and is more prevalent in individuals who have undergone surgical amputation than in those with congenital limb deficiency (Krane and Heller, 1995; Melzack et al., 1997). A recent longitudinal study revealed that PLP occurs more in upper-limb than lower-limb amputees (Bosmans et al., 2010).

Phantom limb pain may have its onset immediately after amputation or years later (Schley et al., 2008). In over three quarters of cases, PLP develops in the first few days following amputation (Krane and Heller, 1995; Parkes, 1973; Jensen et al., 1983). PLP can persist for years and even decades. Gradual decreases in the intensity, severity, and frequency of phantom pain over time are occasionally reported (Jensen et al., 1985; Nikolajsen et al., 1997; Melzack, 1992). However, until now there has been no evidence that the time elapsed since amputation is associated with the occurrence of PLP. Some studies have found no association between the incidence of PLP and the time since amputation (Flor et al., 1995; Wartan et al., 1997). A survey study on the long-term course of PLP in more than 500 war veterans indicated that the pain had not diminished in nearly 50% of the subjects (Wartan et al., 1997). Another large-scale survey in several thousand amputees found that more than 70% of them continued to experience PLP as much as 25 years after the amputation (Sherman et al., 1984).

Most patients with PLP have intermittent pain, with intervals that range from 1 day to several weeks, while a few patients suffer constant pain. The pain often presents itself in the form of attacks that vary in duration from a few seconds to minutes or hours (Wolff et al., 2011). One in four patients experiences PLP for more than 15 hours per day (Sherman et al., 1984).

The most commonly reported modalities of PLP are tingling, burning, and cramping sensations, but many other types of pain, such as throbbing, squeezing, shooting, and stabbing have also been documented (Nikolajsen and Jensen, 2001). The pain tends to be localized distally, regardless of the amputation site (Jensen et al., 1985; Nikolajsen et al., 1997).

In approximately 50% of cases, a phenomenon called ‘telescoping’ occurs, i.e., the distal part of the phantom limb is progressively felt to approach the residual limb, and eventually, it may shrink within the stump (Jensen et al., 1983). Telescoping was assumed to be an adaptive process beneficial to PLP (Cronholm, 1951; Katz, 1992). However, recent evidence suggests telescoping and PLP are positively related (Grüsser et al., 2001; Montoya et al., 1997).

PLP may be elicited or worsened by a range of physical factors (e.g., weather change or pressure on the residual limb) or psychological factors (e.g., emotional stress) (Sherman et al., 1989; Arena et al., 1990). Cognitive factors also play a part in the modulation of PLP. Patients who have personality traits characterized by passive coping are more affected by the pain and report more interference (Richardson et al., 2007).

In summary, PLP can be extremely intractable and disabling. It is sufficiently severe to hamper prosthetic training (Carabelli and Kellerman, 1985) and reduce amputees' likelihood of employment and social activities (Millstein et al., 1985). Apart from its negative impacts on patients' functioning and well-being (Pezzin et al., 2000; Ehde et al., 2000), PLP also poses a significant problem for health care systems worldwide (Hanley et al., 2006). Thus, successful intervention for treatment of PLP is greatly needed.

1.2.2 Neurobiological mechanisms

PLP is usually classified as neuropathic pain, which involves multiple pathophysiological changes, both in the peripheral nervous system (PNS) and in the central nervous system (CNS) (Flor, 2002a; Costigan et al., 2009; Navarro et al., 2007). After surgical removal of a limb, the complete truncation of peripheral nerves and the neural damage initiate a cascade of changes that lead to and sustain phantom pain, which might be the manifestation of maladaptive plasticity in the nervous system (Di Pino et al., 2009). No single mechanism appears to be able to explain the development of PLP independently. Hence, it is currently believed that PLP should be considered a complex syndrome and that multiple mechanisms at different levels in the nervous system contribute to the occurrence of PLP.

Peripheral mechanisms

Following truncation of peripheral nerves, a neuroma is universally formed as a result of aberrant sprouting of regenerating axons. Ectopic discharge from a stump neuroma has been postulated as one important peripheral mechanism. Such neuromas show spontaneous discharge or hyper-excitability following mechanical and chemical stimulation (Devor et al., 1993). In addition, similar abnormal activity and sensitivity occurs in dorsal root ganglia (DRG), where the discharge coming from the residual limb can be amplified (Devor, Seltzer, 1999). In addition, abnormal sympathetic activity may increase the amount of circulating epinephrine, which can trigger and exacerbate neuronal activity from neuroma (Devor et al., 1994). These aberrant nociceptive impulses may be interpreted by the brain as pain.

One of the strongest arguments for a peripheral cause of phantom limb pain is its positive correlation with stump pain. Phantom pain occurs significantly more frequently in amputees with chronic stump pain than in those without stump pain (Sherman and Sherman, 1983). Nevertheless, peripheral factors alone cannot entirely explain the occurrence of PLP. In some cases, PLP occurs immediately after amputation when there are not yet neuromas in the residual limb (Carlen et al., 1978). Congenital amputees occasionally also report PLP (Alviar et al., 2011). These findings indicate that central factors must be involved as well.

Central mechanisms

While spinal plasticity, such as sensitization of low-threshold sensory receptors (Cervero, 2009) and central sensitization (Costigan et al., 2009; Baron, 2006), have been discussed as processes involved in PLP or neuropathic pain, cortical reorganization has gained a great deal of attention and is considered a plausible explanation for PLP. Furthermore, cortical reorganization may partly account for why stimulation on the face, stump or surrounding regions elicit sensations referred to the phantom limb (Flor et al., 2006).

Extensive empirical studies have demonstrated that sensorimotor cortices undergo massive neuroplasticity changes in people with extremity amputation (Flor et al., 1995; Ramachandran et al., 1992; Hall et al., 1990; Chen et al., 2002). The cortical area that formerly represented the amputated extremity has been found to be taken over by its neighboring mouth and chin representation zone in the primary somatosensory cortex (S1) of amputees (Elbert et al., 1994; Yang et al., 1994). Further studies have found that cortical reorganization also develops in the motor cortex (M1) (Lotze et al., 2001; Karl et al., 2001; Karl et al., 2004).

Furthermore, the extent of cortical reorganization has been found to be closely associated with the severity of phantom pain and the size of the deafferented region. A series of studies have revealed a positive relation between the magnitude of PLP and the amount of reorganization in the sensorimotor cortices (Lotze et al., 2001; Karl et al., 2001; Karl et al., 2004; Florence et al., 2000). Cortical remapping may be related to the incongruence of motor intentions and sensory feedback, based on maladaptive plastic changes in the brain (Diers et al., 2010).

Neuroplasticity has also been observed in the thalamus and has shown close relation to the perception of phantom limbs and phantom pain, according to the results of thalamic stimulation and recordings in human amputees (Davis et al., 1998). Experiments in monkeys have shown that the changes can be relayed from the spinal and brainstem level (Florence and Kaas, 1995), but those on the subcortical levels may also originate in the cortex, which has strong efferent connections to the thalamus and lower structures (Ergenzinger et al., 1998).

1.2.3 State-of-the-art treatments for PLP

Commonly used treatments for PLP can be categorized as pharmacological, surgical, anesthetic, psychological, or other methods (Flor, 2002a). The following is a brief description of each category.

Pharmacological

Numerous pharmacological interventions have been reported, such as N-methyl D-aspartate receptor antagonists, antidepressants, anticonvulsants, neuroleptics, β-blockers, and muscle relaxants (Wolff et al., 2011; Alviar et al., 2011). Despite many drugs or combination of drugs tried over decades, mixed results have been obtained, with some studies showing positive outcomes and others showing no efficacy (Alviar et al., 2011).

Surgical

Conventional surgical methods include stump revision, neurectomy, rhizotomy, cordotomy sympathectomy, tractotomy etc (Flor, 2002a). In general, these treatments have shown unfavorable results for decades and have been most abandoned, as the surgical procedures may carry a risk of further nerve damage (Nikolajsen and Jensen, 2001).

Neurostimulation based on surgery is also grouped in this category. Deep brain stimulation (DBS) of the periventricular grey (PVG) and sensory thalamus has shown promise as an effective treatment for peripheral neuropathic pain and PLP (Bittar et al., 2005; Owen et al., 2007; Ray et al., 2009; Nguyen et al., 2011). Relief of PLP has also been achieved by spinal cord stimulation (SCS) and motor cortex stimulation (MCS) (Katayama et al., 2002; Sol et al., 2002). While neurostimulation appears to be promising, it is currently difficult to assess its effectiveness because of the lack of long-term controlled studies.

Anesthetic

Many studies have examined the effectiveness of epidural anesthesia but unfortunately have not been consistent in their experimental designs and have yielded inconsistent results (Gehling and Tryba, 2003; Lambert et al., 2001). Other anesthetic methods, including nerve blocks, sympathetic blocks, and local anesthesia, have also been used, while no well-controlled studies have demonstrated long-lasting favorable effects on diminishing PLP.

Psychological

Several studies have suggested that temperature and electromyography (EMG) biofeedback may be helpful in alleviating burning and cramping PLP sensations (Belleggia and Birbaumer, 2001; Dougherty, 1980; Sherman et al., 1979). However, there is no evidence to match specific types of phantom pain with specific biofeedback techniques (Harden et al., 2005). Hypnosis has also been anecdotally reported as being effective in PLP relief (Chan, 2006).

Other approaches

Transcutaneous electrical nerve stimulation (TENS) has been recommended as a treatment option for phantom pain and stump pain (Black et al., 2009). In multiple placebo-controlled trials and epidemiologic surveys (Wartan et al., 1997; Baron, 2006; Halbert et al., 2002), desensitization resulting from TENS application has been reported to be capable of relieving PLP. However, its long-term effectiveness remains unclear. Some studies have suggested that PLP reductions after 1 year of TENS treatment are comparable to those achieved using placebos (Sherman 2002).

Mirror therapy appears to be a promising treatment option. In mirror therapy, patients are given the visual illusion that they can use their missing limbs again (Ramachandran and Rodgers-Ramachandran, 1996; Chan et al., 2007). Recently, a randomized, sham-controlled, crossover study of mirror therapy indicated that it achieved a significant decrease in pain intensity, whereas two control groups did not show satisfactory treatment outcomes (Chan et al., 2007). Despite the success of this therapy, the underlying mechanism accounting for the success remains to be elucidated, and more experiments are needed to replicate the results.

Many other treatments for PLP, such vibration, acupuncture, mental imagery, ultrasound, massage, electroconvulsive therapy, electromagnetic fields, and far infrared rays, have been reported in small-sample-size studies and case reports (Chan, 2006; Lundeberg, 1985; Mannix et al., 2013; MacIver et al., 2008; Rasmussen and Rummans, 2000; Huang et al., 2009; Bókkon et al., 2011). Although many therapies for PLP have been attempted or are currently in use, most appear ineffective or limited in their effectiveness. It is thus critical to develop effective treatments for PLP.

1.3 Sensory feedback

1.3.1 Sensory feedback for PLP treatment

Behaviorally relevant interventions that provide feedback to the brain may modify the cortical mapping in brain areas such as the primary somatosensory cortex (S1). In the adult owl monkey, several weeks of tactile discrimination training of individual fingers led to an expansion of the cortices representing the trained fingers in the S1 zone, whereas cortical alteration was not observed after passive stimulation (Jenkins et al., 1990). Change in the topographic organization of the hand representation zone was also observed after training in a frequency discrimination task (Recanzone et al., 1992).

Phantom limb pain has been found to be related to reorganization in S1. There is a significant correlation between the severity of PLP and the amount of cortical reorganization (Grüsser et al., 2001; Knecht et al., 1996). It therefore has been postulated that interventions designed to reverse somatosensory cortical reorganization may be valuable alternative treatments for PLP and neuropathic pain (Flor, 2002b). Providing cognitive behavior-relevant sensory feedback may be able to address the incongruence between motor intention and sensory feedback and consequently relieve phantom pain through normalization of cortical somatosensory representation maps.

Several studies have demonstrated the beneficial effect of enhancing somatosensory feedback on PLP and cortical reorganization. In a study on the effect of sensory discrimination training on PLP, amputee patients were asked to perform the task of discriminating among the locations and frequencies of the surface electrical stimuli applied to the residual limb. After two weeks of daily training, all five patients in the training group experienced significant decreases in PLP, compared with a control group that received regular treatments. Their discrimination ability was also improved, and the amount of cortical reorganization was reduced (Flor et al., 2001). In another study, intensive use of myoelectric prosthesis led to significant reduction in PLP (Lotze et al., 1999). It has also been reported that training for control of a robotic hand with a limited amount of sensory feedback significantly reduced PLP in a human amputee implanted with four intra-fascicular electrodes in the nerve stump. The reduction in PLP lasted several weeks after removal of the electrodes, and changes in sensorimotor cortex topography were observed (Rossini et al., 2010). A recent study found that usage of a prosthesis that provides somatosensory feedback on the grip strength was effective in alleviating PLP (Dietrich et al., 2012). Furthermore, tactile discrimination, rather than passive stimulation, relieved pain and improved tactile acuity in patients with chronic pain (Moseley et al., 2008). These findings suggest the therapeutic benefit of somatosensory feedback in the treatment of PLP and chronic pain.

1.3.2 Means of providing sensory feedback

Although sensory feedback has been proposed for the treatment of PLP, it was first recognized as being greatly needed for better control of prosthetic devices and improving body awareness of artificial limbs. Artificial sensory feedback is intended to provide users who have lost their sensory functions with regained tactile and kinesthetic sensibilities. For decades, the development of artificial sensory inputs to a sensory feedback system for prostheses has been mainly based on mechanical stimulation, electrocutaneous stimulation, and direct nerve stimulation.

Mechanical stimulation

Mechanical stimulation, which can be applied in two ways, by vibration or by static pressure, conveys sensory information by activation of mechanoreceptors in the skin using an actuator (Kaczmarek et al., 1991). Mechanical sensory feedback systems generally have higher universal psychological acceptance than electrocutaneous systems because the vibration and pressure sensation feel more natural. While mechanical transducers have occasionally been criticized as being bulky, heavy, moving, and power-consuming, a comparative study suggested that it is capable of yielding performance comparable to electrocutaneous stimulation (Shannon, 1976). In several studies, different types of small, low-power motors were evaluated successfully for application in shoulder pad displays (Toney et al., 2003) and sensory feedback in prosthetic systems (Pylatiuk et al., 2006; Witteveen et al., 2012).

Electrocutaneous stimulation

In electrocutaneous stimulation, electrical current flows through the skin and evokes sensations by directly activating afferent nerve fibers (Szeto and Saunders, 1982). It has also been suggested that small electrodes (1 mm^2) activate receptors or end organs in the dermis (Pfeiffer, 1968). Subjects describe the qualities of the sensations evoked by electrocutaneous stimulation as tingles, itches, vibrations, buzzes, touches, pressure, pinches, and sharp and burning pain. The sensations originate in the skin but are not necessarily confined to a small region of skin when deeper nerve bundles are stimulated. The sensation evoked is a function of many factors, including the stimulating voltage, the current, the waveform, the electrode size, the material, the location on the skin, the thickness, and the degree of hydration (Kaczmarek et al., 1991).

The use of electrocutaneous stimulation to generate sensory feedback has attracted great attention because of its ability to provide densely packed information and produce a sensation whose frequency and intensity can be reliably controlled (Szeto and Saunders, 1982). Unlike mechanical vibrators, cutaneous electrodes usually have no moving parts and maintain constant contact with the skin. In addition, they are efficient in terms of power consumption and are simple to fabricate (Szeto and Saunders, 1982). A series of studies have shown that sensory feedback employing electrocutaneous stimulation improves the level of a subject's confidence in using a hand prosthesis and facilitates the incorporation of the prosthesis into body image (Scott et al., 1980; Prior et al., 1976; Shannon, 1979; Schmidl, 1977; Beeker et al., 1967).

Intra-neural stimulation

When electrical stimulation is applied directly to the nerve in a residual limb, possible activation of small clusters of sensory neurons at a subfascicular level may evoke more natural, meaningful sensations. This was demonstrated in a study in human amputees with micro-fabricated longitudinal intra-fascicular electrodes (LIFE) implanted in their median/ulnar nerve stumps. The stimulations generated discrete, graded sensations of touch/pressure, joint position or movement of the phantom hand, although the proprioceptive perceptions were reported to be vague, and the interpretation was therefore difficult (Dhillon et al., 2005). A recent study used newer-generation, thin-film LIFEs with more stimulating channels implanted in the median/ulnar nerves of an amputee volunteer for four weeks. The results showed that during the initial experiments, the patient reported various sensations after stimulation at low to moderate levels, although tactile sensations could only be generated within the first 10 days (Rossini et al., 2010). Although many problems, including development of biochemically resistant electrodes with high selectivity and evaluation of long-term effects, remain to be investigated, intra-neural stimulation might be another viable means of artificially providing sensory feedback in the future.

1.3.3 Measurement of sensory feedback

Cutaneous sensory feedback is essentially the transmission of sensory information from the skin to the brain. Electrocutaneous stimulation activates sensory neurons in or under the skin. Neural signals passing via sensory nerves to the brain evoke subjective experience of the stimulus and produce a sensation. Psychophysical methods can be used to quantitatively investigate the relation between electrical stimuli and subjective sensations (Gescheider, 1997).

Measurement of the perception threshold is usually the first step in design of a sensory feedback scheme because the stimulus current amplitude between the perception threshold and the upper limit should be carefully determined. Since the perception threshold is a function of the electric charge in the context of electrocutaneous stimulation, a lower threshold is preferred for its better energy efficiency (Szeto and Saunders, 1982). Among the three classical psychophysical methods for perception threshold measurement (i.e., the method of adjustment, the method of limits, and the method of constant stimuli), the method of constant stimuli is generally considered to provide the most reliable estimate of the threshold because a random presentation of stimuli can efficiently eliminate possible bias from a subject's anticipation (Ehrenstein and Ehrenstein, 1999).

In a sensory feedback scheme, evoked sensation ideally should be strong but without discomfort. Measurement of a sensation involves evaluation of the sensation quality (or type) and estimation of the sensation intensity.

The qualities of the sensations evoked by cutaneous electrical stimulation have been documented in the literature mainly in the forms of descriptive words reported by subjects, such as touch, pressure, tingling, and vibration. As a general rule in psychophysics, questions that are precise and simple enough to obtain convincing answer should be formulated (Ehrenstein, 1999). Therefore, a question that provides subjects with a group of descriptors covering possibly elicited sensation types may be used to evaluate the quality of sensation.

The intensity of sensation can be quantitatively estimated using a scaling method by assigning numbers to the perceptual event such as sensation (Stevens, 1957). A visual analogue scale (VAS) can be used to measure a sensation, with 0 representing 'no sensation' and 10 representing 'the upper limit of the sensation or pain.' There are also a number of other types of linear scales, such as the Likert scale and the Borg scale, which may outperform others in specific circumstances (Grant et al., 1999).

1.4 The EU TIME project

Part of this PhD research was involved in the EU consortium's TIME project. The goal of the TIME project was to develop an implantable neural prosthesis system with sufficient stimulation selectivity to manipulate phantom sensations and explore the possibility of using the method as a potentially effective treatment for PLP. Given sufficient control over a large set of afferent fibers and fiber types, stimulation via a neural interface is able to artificially evoke sensations of touch, vibration, heat, and illusions of limb/ finger/joint position and movement. In the case of amputees, precise activation of the intact part of the transacted sensory fibers through a selective multi-channel electrode may elicit vivid sensations in the phantom limb. The TIME project hypothesizes that manipulating phantom sensations using selective stimulation of the nerve stump may mitigate PLP and reverse cortical reorganization. The hypothesis is illustrated in Figure 3.

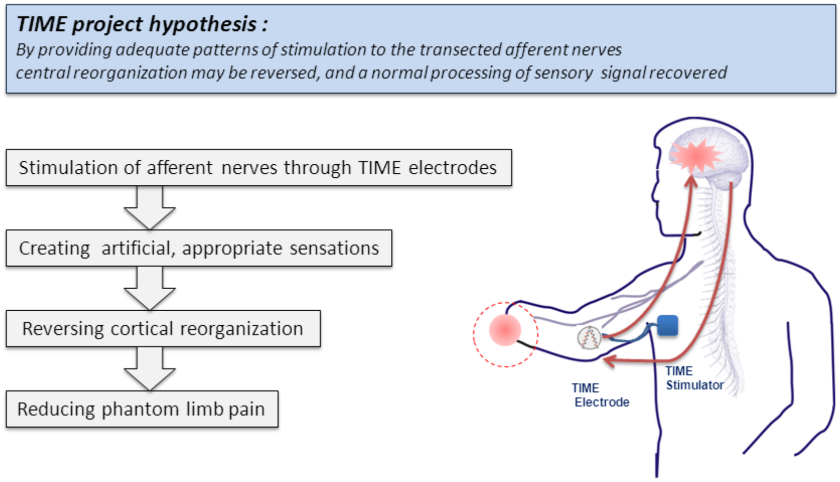

Figure 3. Illustration of the hypothesis in the TIME project.

The TIME project consists of three core technological challenges: (1) development of a novel micro-fabricated neural interface—the Thin-film Intrafascicular Multichannel Electrode array (TIME)—to be implanted in the nerve stump, (2) development of a human-implantable multichannel stimulator system, and (3) development of a psychophysical testing platform that can support effective and efficient evaluation of phantom sensations evoked by multi-channel selective micro-stimulation.

Because the optimal set of stimulation patterns that can generate natural phantom sensations has not been well identified in the literature, various combinations of stimulation parameters were considered. A TIME electrode array features up to 12 active contact sites (Boretius et al., 2010). Different combinations of stimulus parameters in the TIME multichannel system can result in a wide range of possible stimulation patterns. In a clinical trial, to reduce a patient's mental load and avoid habituation to the stimulation, it is important to test a large number of stimuli efficiently within a limited experiment time. Therefore, an automated stimulation and evaluation process is necessary to minimize the time needed to collect the measurement data from the patient. A computerized platform can support the automated process of stimulation and evaluation. Design and implementation of the TIME psychophysical testing platform constitutes part of the PhD work.

2. Overview of the PhD work

2.1 Hypothesis and questions

As stated in the previous section, the severity of PLP was found to be positively associated with the amount of cortical alteration (Grüsser et al., 2001). Because cortical changes in the brain may result from the incongruence of motor intention and impaired sensory feedback due to transection of periphery nerves (Diers et al., 2010), artificially providing adequate feedback of the phantom limb may assist in addressing the incongruence. The scientific hypothesis of the present PhD research was the following:

> *Providing sensory feedback through electrocutaneous stimulation of a residual limb may reverse cortical alteration and consequently reduce PLP.*

To test the hypothesis, three questions were formulated:

Question 1. How do stimulus parameters influence sensory responses?

Question 2. Does sensory identification training have a therapeutic benefit for PLP?

Question 3. How may sensory feedback be evaluated efficiently in a multi-channel stimulation setting?

The sensation elicited by electrocutaneous stimulation is a function of the stimulation parameters. The stimulus parameters selected to be modulated to convey sensory information play important roles in determining the effectiveness of a sensory feedback scheme. It is thus important to examine how stimulus parameters influence sensory responses (Question 1). Furthermore, training patients in discriminating among different stimulus parameters has been proven to have a positive effect on PLP (Flor et al., 2001). Sensory identification is a moderately more complex behaviorally relevant task that is assumed to involve more sophisticated sensory processing. Does sensory identification training have a therapeutic benefit for PLP (Question 2)? Given the multichannel, intra-neural stimulation system developed in the TIME project, how may sensory feedback be evaluated effectively and efficiently (Question 3)?

Electrocutaneous stimulation, rather than mechanical stimulation, was chosen as the means of delivering sensory feedback, mainly for the following reasons: (1) it is likely to produce more types of sensation, which may involve more sensory processing and thus act on the sensory cortices more effectively; (2) stimulation parameters are more controllable, which partly ensures the reliability of the sensory feedback; and (3) many product options for electrodes are commercially available.

2.2 Studies and corresponding publications

To address the three questions raised, five studies were conducted in this PhD research. Question 1 was addressed through examination of the impact of stimulation parameters on the perception threshold in Study 1 and the impact on evoked sensation magnitude, quality, and location in Study 2. Question 2 was addressed in Studies 3 and 4. Study 3 investigated human ability to identify the stimulation location and pulse number in behaviorally relevant tasks with able-bodied subjects. In study 4, an upper-limb amputee volunteer with PLP was trained in sensory identification to examine the effect of training on identification performance, the intensity of PLP, and cortical reorganization. Question 3 was addressed by design and development of a computerized, automated psychophysical test platform in Study 5. An overview of the objectives, subjects, and methodologies of the five specific studies is presented in Table 1.

Table 1. Overview of the five studies conducted in this PhD research, including objectives, subjects, and methodologies.

Study	Objective	Subject	Methodology
Study 1	*Investigation of the impact of selected stimulation parameters on the perception threshold*	12 able-bodied	***Electrodes***: Five solid-gel Ag/AgCl electrodes. ***Placement***: 5 cm from the elbow crease, evenly distributed around the left forearm. ***Measure***: Perception threshold ***Investigated parameters***: location, number of active electrodes, number of pulses, and interleaved time between a pair of electrodes.
Study 2	*Evaluation of the impact of selected stimulation parameters on evoked sensations*	16 able-bodied	***Electrodes***: same as study 1. ***Placement***: same as study 1. ***Measure***: sensation modality, location, quality, and magnitude ***Investigated parameters***: same as study 1
Study 3	*Examination of the sensory identification ability of able-bodied subjects*	10 Able-bodied	***Electrodes***: Three solid-gel Ag/AgCl electrodes. ***Placement***: 5 cm from the elbow crease, on the volar side of the left forearm. ***Measure***: identification performance ***Tasks***: Identification among five stimulation locations; identification among 5 pulse numbers; or identification among 10 paired combinations of stimulation location and pulse number.
Study 4	*Exploration of the effect of sensory identification training on PLP and cortical reorganization*	1 Upper-limb amputee	***Electrodes***: Eight solid-gel Ag/AgCl electrodes ***Placement***: on the stump such that the evoked sensations referred to different locations in the phantom hand. ***Treatment***: daily 1-hr training consisted of three sessions in which the subject was asked to identify: • Stimulating site • Number of pulses (1, 2, 5, 10, and 20) • Combination of location and pulse number ***Measure***: PLP (VAS), accuracy of sensory identification, and cortical reorganization (high-density EEG).
Study 5	*Design and development of a computerized tool to control and evaluate multi-channel electrical stimulation-based sensory feedback*	NA	***Functionality:*** A. Stimulator and experiment control (SEC) • Configure stimuli. • Control experiment • Monitor the experimental progress B. Interactive subject interface (ISI) • Threshold measurement • Sensation measurement • Collect the measurement data *C.* Communication between SEC and ISI to achieve the automated process of stimulation and sensation evaluation.

Study 1: Investigation of the impact of selected stimulation parameters on the perception threshold

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Impacts of selected stimulation patterns on the perception threshold in electrocutaneous stimulation

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Study 2: Evaluation of the impact of selected stimulation parameters on evoked sensations

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Evaluation of sensation evoked by electrocutaneous stimulation on forearm in nondisabled subjects

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Study 3: Examination of the sensory identification ability of able-bodied subjects

Under preparation, to be submitted to Journal of Neuroengineering and Rehabilitation.

Human ability in identification of location and pulse number for electrocutaneous stimulation applied on the forearm

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Study 4: Exploration of the effect of sensory identification training on PLP and cortical reorganization

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A case study on phantom sensation and sensory discrimination induced by electrocutaneous stimulation

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Study 5: Design and development of a computerized tool to control and evaluate multi-channel electrical stimulation-based sensory feedback

Under preparation, to be submitted to International Journal of Computer Human Interaction.

Computerized tool to control and evaluate multi-channel electrical stimulation based sensory feedback—example of use for phantom limb pain treatment

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3. Discussion and Conclusion

Five studies were performed to address the hypothesis and the three formulated questions. The main outcomes and related issues of the Ph.D. research have been discussed here, whereas a more detailed discussion of specific studies can be found in relevant papers. Some perspectives pertaining to this research topic are also discussed, as appropriate.

3.1 Discussion of main findings

An overview of the main findings of each study is outlined in Table 2.

Table 2. Major outcomes for each study.

	Overall hypothesis: *Providing sensory feedback through electrocutaneous stimulation of a residual limb may reverse cortical alteration and consequently reduce PLP.*		
	Q1: *How do stimulation parameters influence sensory input?*	***Q2:*** *Does sensory identification training have therapeutic benefit for PLP?*	***Q3:*** *How may sensory feedback be evaluated efficiently in a multi-channel stimulation setting?*
Study 1*: Investigation of the impact of selected stimulation parameters on the perception threshold*	• Ventral side has a lower perception threshold than dorsal side of the forearm. • There is an inverse relationship between the perception threshold and the number of pulses in a pulse train.		
Study 2*: Evaluation of the impact of selected stimulation parameters on evoked sensations*	• Volar and ulnar side of the forearm can perceive more consistent tactile sensation. • The number of pulses in a pulse train significantly influences the intensity of evoked sensations.		
Study 3*: Examination of the sensory identification ability of able-bodied subjects*		The average performance in sensory identification of location and pulse number was promising (92.2% and 90.8%).	
Study 4*: Exploration of the effect of sensory identification training on PLP and cortical reorganization*		The sensory identification accuracy improved over the training period, but there was no decreases in PLP and no change in cortical plasticity.	
Study 5*: Design and development of a computerized tool to control and evaluate multi-channel electrical stimulation-based sensory feedback*			The platform was utilized for threshold and sensation measurement with intra-fasicular multi-channel electrodes implanted in the nerve stump in an amputee volunteer.

In summary, the ventral forearm had a lower perception threshold than the dorsal forearm. The stimulation location on the forearm significantly influenced the sensory responses. The number of pulses also had a significant impact on the perceived magnitude of sensation. When the stimulation location and pulse number were varied in identification tasks, satisfactory identification performance was achieved by able-bodied subjects. However, training in the same sensory identification tasks neither relieved PLP nor reversed cortical reorganization in the amputee patient, although the amputee patient's identification performance improved over the training period. In addition, a computerized sensory feedback evaluation platform developed for the TIME project made a tool for further studies on PLP treatment by providing patients with more intuitive, natural sensory feedback using selective intra-neural stimulation. Each study is discussed below in relation to the three questions.

Study 1: Effect of stimulation parameters on the perception threshold (Q1)

By examining the relation between stimulation parameters and the perception threshold, study 1 provided useful information for optimization of a stimulation protocol in a sensory feedback scheme. The ventral aspect of the forearm was found to have a lower perception threshold than the dorsal aspect. Therefore, use of the ventral forearm is recommended for receiving electrocutaneous sensory feedback, due to the better energy efficiency and potentially higher information transfer capacity that it provides.

Sensory feedback should be consistent to gain users' confidence in interpreting artificial sensory input. However, consistency cannot be guaranteed because of the non-linear relation between the stimulation parameters and sensory responses (Pfeiffer, 1968). This is confirmed by the results of study 1. The four parameters investigated—stimulation location, number of stimulating channels, number of pulses, and time delay in interleaved stimulation—were all shown to be related to the perception threshold in a non-linear way.

The stimulation parameters investigated were chosen on the basis of a literature review and the need for sensory feedback in amputee patients. Some parameters, such as body locus, pulse duration, waveform, and frequency, have been investigated in previous studies (Girvin et al., 1982; Kantor et al., 1994; Palmer et al., 1999). Those studies mainly concerned single-channel stimulation using different types of surface electrodes at various body sites, whereas study 1 investigated the parameters in relation to multi-channel stimulation on the forearm with solid-gel electrodes.

Study 2: Effect of stimulation parameters on evoked sensation (Q1)

Study 2 provided information used in the choice of the optimal stimulation parameters to be used for sensory modulation. Varying a stimulation parameter can modulate the sensation by which information is encoded and transmitted to human subjects (Szeto and Saunders, 1982). If the sensation (e.g., intensity or modality) can be easily and reliably modulated by varying a stimulation parameter, the coding scheme was assumed to be effective.

In study 2, stimulation of the ventral forearm was found to more easily evoke tactile and less pricking sensation than stimulation of the dorsal side. This finding is important to ensure the comfort of electrocutaneous sensory feedback, as electrical stimulation is often associated with discomfort and occasionally pain, which can be a limiting factor in users' acceptance (Chae and Hart, 1998; Garnsworthy et al., 1988). Other elements, such as electrode size, waveform, and frequency, may also have an impact on the comfort of electrocutaneous stimulation (Kuhn et al., 2010; Naaman et al., 2000; Gracanin and Trnkoczy, 1975).

Furthermore, the number of pulses has a significant effect on the perceived magnitude, implying that varying the number of pulses may be an effective means of sensory modulation. This finding is consistent with those of a recent study (Van Der Heide et al., 2009). An early study derived a specific relation for pulse number growing as the 1.8 power of the perceived magnitude in stimulation applied on the abdomen at 30 Hz (Sachs et al., 1980).

Study 3: Sensory identification in able-bodied subjects (Q2)

In study 3, the sensory identification ability of able-bodied subjects was evaluated. Based on the findings of studies 1 and 2, electrodes were placed on the ventral forearm. The stimulation location and pulse number were varied for purposes of sensory modulation.

Modulation of the two parameters yielded satisfactory identification performance. The overall accuracy was 92.2% for spatial identification and 90.8% for the identification of the pulse number. Performance worsened when the two dimensions were required to be distinguished at the same time. The results provide an opportunity to directly compare the identification performance of able-bodied subjects and amputees, which can assist in translating the findings to clinical application. However, to the best of my knowledge, there have been no such studies on sensory identification with upper-limb amputees. The only related work has been on the effect of sensory discrimination training on PLP. In that study, amputee subjects were trained in sensory discrimination of stimulation location and frequency. Discriminability was shown to be improved over the two weeks of the training period, but the accuracy remained below 60% for both location and frequency discrimination (Flor et al., 2001).

Study 4: Sensory feedback training in amputee patients (Q2)

In study 4, an amputee patient was trained in sensory identification to investigate the effect of training on PLP. The stimulation location and pulse number were again varied for purposes of sensory modulation. It was expected that the identification ability of amputees would be better than that of able-bodied subjects because stimulation of the residual limb can evoke sensations not only locally but also referred to the phantom limb (Ramachandran et al., 1992), implying that the somatosensory cortex representing the forearm may be expanded and thus that sensory acuity may be improved in amputees. However, the amputee patient did not achieve good identification performance in the first days of training. Over the training period, the amputee patient's accuracy improved and was eventually comparable to that of the able-bodied subjects. The unexpected low identification ability of the amputee patient at the beginning of the training period was likely due to subject-to-subject variance in learning rates. Research into the identification abilities of more amputees is needed to allow for statistical comparison between the two groups.

No reduction in PLP and no changes in cortical reorganization were observed after ten days of training. Nevertheless, the failure of sensory identification training in PLP treatment should be interpreted with caution. First of all, the training might not have been extensive enough, or the stimulus intensity might not have been sufficiently strong. A similar study on the effect of feedback-guided sensory training on PLP was performed with ten daily 90-min training sessions and a stimulus level of 0.1 mA below the individual pain threshold (Flor et al., 2001). In that study, all five amputee patients experienced reductions in PLP and reversal of cortical reorganization. A comparative study is needed to validate the training regimen. Furthermore, cortical reorganization alone might not be the primary factor in the development of PLP in this patient. Providing sensory feedback of the phantom hand with the aim of counteracting cortical reorganization might thus be ineffective for him. This may further confirm that various mechanisms account for the causation and maintenance of PLP in individual patients and that no one treatment is likely to be effective for all amputee patients (Flor, 2002a). Appropriate selection of interventions that can address the underlying problems will be important for effective PLP treatment.

A follow-up study with a larger sample size and perhaps a higher stimulation intensity is needed to further evaluate the effect of sensory identification training on PLP. Additionally, in what subgroup of amputee patients, sensory feedback-based intervention is effective remains to be investigated. To what extent the number of training sessions and the stimulus intensity would affect the treatment outcome also needs to be determined.

Study 5: Computerized psychophysical testing platform (Q3)

Recently, peripheral intra-neural interfaces with multiple channels have been developed for direct nerve stimulation with high selectivity, which could be used to record motor signals in bionic hand control (Rossini et al., 2010; Boretius et al., 2010; Dhillon and Horch, 2005). Using the same electrodes to selectively activate sensory fibers in the nerve bundle provides the possibility to manipulate phantom sensation (Dhillon and Horch, 2005) and counteract phantom pain by enabling sensory processing that is missing subsequent to amputation.

To efficiently evaluate the phantom sensation evoked by a wide range of stimulation patterns in a multi-channel setting, a computerized psychophysical testing platform was developed. The platform was designed to collect the data from the threshold and sensation measure experiments. However, to counteract cortical alterations and consequently relieve PLP, it was expected that repeated stimulation sessions with one subject would need to be carried out. Hence, selection of a subset of optimal stimulation patterns was required for each subject, based on the results of the sensation measurements. Optimal stimulation patterns were defined as those that elicited clear, distinct types of sensations referred to the phantom limb. Therefore, a module that can automatically select optimal stimulation patterns should be considered in future development.

3.2 Methodological considerations

Studies with able-bodied subjects

The first three studies were conducted with able-bodied subjects. It is noteworthy that the sample population is not representative of amputee patients with PLP. Therefore, the results ought to be carefully interpreted before implementation in amputee patients, because when stimulating damaged limbs, the perceptual experience may differ from those in nondisabled people. It will be of interest to see whether similar results can be obtained with subjects with amputations in future work.

Choice of stimulation parameters

Throughout studies 1 to 4, a biphasic waveform was used because the dermis accumulates electrochemical changes from monophasic pulses. In addition, biphasic pulse pairs produce less long-term reddening and a more comfortable sensation than monophasic pulses (Szeto and Saunders, 1982). A pulse duration of 200 µs was chosen because it produced the least ‘pricking’ sensation in our pilot experiment, in which pulse durations of 100 µs, 200 µs and 500 µs were tested. A frequency of 20 Hz was used (Szeto et al., 1979) because this may be the optimal frequency for sensory communication, as the maximum frequency discrimination occurs near 20 Hz (Szeto et al., 1979).

Stimulation parameters related to dual channel stimulation were investigated in studies 1 and 2 because incorporation of a second channel introduces additional variables that can affect the efficacy of sensory feedback (Szeto and Saunders, 1982). As a limitation, only a selected set of stimulation parameters (i.e., the stimulation site, the number of stimulating channels, the number of pulses, and the time delay between two channels) were examined in studies 1 and 2.

Sensory identification

Both animal and human experiments have revealed that training in sensory discrimination, rather than passive stimulation, can result in cortical remodeling (Recanzone et al., 1992; Flor et al., 2001). In discrimination tasks, a subject needs to determine whether there is a detectable difference between the presented stimulus and the reference stimulus. In identification tasks, the subject needs to identify the presented stimulus among several different stimuli. Sensory identification requires not only detecting the difference between two stimuli presented but also determining which stimulus was presented. As such, it is assumed that sensory identification involves more advanced cognitive activity, such as attention and memory, than does sensory discrimination or passive stimulation and consequently facilitates cortex remapping. This assumption led to studies 3 and 4, in which sensory identification was chosen as the means of providing sensory feedback to the subjects.

Measurement of cortical reorganization

In the study 4 on the effect of sensory identification training on PLP, cortical reorganization was assessed before and after training. Neuroelectrical source analysis of high-density EEG recording was used to localize the cortical activity. Light superficial pressure stimulation was applied to the corner of the lower lip because the cortical area representing the mouth was found to take over the former hand area (Ramachandran et al., 1992; Elbert et al., 1994). The patient’s phantom pain and the observation of the shift of the lip area to the hand area on the amputation side confirmed the earlier proposed theory that cortical reorganization is related to PLP (Grüsser et al., 2001; Flor et al., 2001; Birbaumer, 1997).

However, the PLP was not reduced after the sensory identification training, and the cortical shift was not reversed. From the perspective of the technology employed, although EEG source analysis is occasionally used to localize brain activity, it suffers from the limitation of poor spatial resolution. The accuracy of EEG source analysis is affected by many practical factors, such as the electrode position on the scalp, the choice of reference, the interpolation algorithm chosen, the treatment of artifact-contaminated channels due to poor electrode–scalp contact or amplifier malfunction, and the head model and mathematical inverse model chosen (Michel et al., 2004). In this regard, other imaging methods, such as fMRI, might be better suited to localization of brain activity and ensure the validity of the results.

Electrocutaneous vs. intra-neural sensory feedback

Sensory feedback employing electrocutaneous stimulation has been shown to be somewhat successful in PLP treatment (Flor et al., 2001; Dietrich et al., 2012). Its noninvasiveness is also attractive. However, electrocutaneous stimulation can only elicit somatic sensation (e.g., touch, tingling) locally or in the phantom limb, which greatly limits the utilization of sensory feedback. Performing behaviorally relevant discrimination and identification tasks is then used as an alternative means of providing meaningful sensory feedback. Incorporation of other sensory modality feedback (e.g., visual, audio) may enhance its effectiveness in counteracting the cortical reorganization underlying PLP.

Direct nerve stimulation made it possible to evoke more types of meaningful sensory feedback (e.g., finger movement, joint position, wrist movement) (Dhillon et al., 2005). Moreover, it has the advantage of using the same set of implanted electrodes for both bionic hand control and sensory feedback. In particular, the patient who participated in study 4 was later treated by providing sensory feedback using intrafascicular stimulation with implanted TIME electrodes, and PLP was temporarily alleviated within the implantation period (results not published). This is an exciting clue that encourages further exploration of this type of sensory feedback in PLP treatment.

3.3 Conclusions

This PhD thesis has presented five studies to address the hypothesis that providing sensory feedback through electrocutaneous stimulation of a residual limb may reverse cortical alteration and consequently reduce PLP in amputee patients. The impact of stimulation parameters on the perception threshold and the evoked sensation was examined. The stimulation location and pulse number were identified to be able to effectively convey sensory information. Human ability in sensory identification of the two parameters was then investigated, and satisfactory performance was obtained in able-bodied subjects. On the basis of these findings, the hypothesis was tested by providing sensory identification training to an upper-limb amputee volunteer. However, PLP and cortical reorganization in this patient did not show significant changes. Direct afferent nerve stimulation of the residual limb makes it possible to evoke natural sensations referred to the phantom limb. As part of the EU-funded TIME project, a computerized tool was developed for efficient sensory feedback evaluation in a multi-channel direct nerve stimulation system that may be used to provide more meaningful sensory feedback to amputee patients and consequently reduce PLP. Using sensory feedback to treat PLP or other chronic pain is still at an early stage of development. Multiple sensory modality feedback could also be considered as the focus of future work.

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