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THE INFLUENCE OF VISUAL FEEDBACK IN PHANTOM LIMB PAIN AND PERCEPTION – APPLICATION OF A NOVEL AUGMENTED REALITY PLATFORM IN BASIC RESEARCH AND TREATMENT

BY
MIKKEL THØGERSEN

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The influence of visual feedback in phantom limb pain and perception – Application of a novel augmented reality platform in basic research and treatment

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Curriculum Vitae

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Mikkel holds a B.Sc. and M.Sc. in computer vision and electronics engineering from the faculty of engineering and science at Aalborg University, Denmark. Following a short period working in industry, he enrolled as a PhD fellow working at the Center for Neuroplasticity and Pain in the Integrative Neuroscience group under the supervision of Associate Professor Laura Petrini. His main areas of research are mixed reality systems with a focus on their use in medical applications.

Abstract

The phantom limb pain condition has been puzzling researchers for decades. Despite that it is a well-studied and common ailment for amputees, its origin and treatment is still unclear. In the previous two decades, the dominant hypothesis in the field has been that maladaptive reorganizations happen in the cortex, as a result of deafferentation and ultimately results in phantom pain. While it remains a question whether these reorganizations are causal, many new strategies to treat phantom limb pain are based on this hypothesis. This line of treatments were pioneered by the mirror box illusion, wherein amputees could see a recreated visualization of their lost limb. The aim of using this illusion has been to recreate sensory feedback to stimulate the dormant cortical representation of the lost limb, and thereby reverse the maladaptive cortical changes. In a recent study, the efficacy of the mirror illusion was investigated. The authors found that pain relief had a significant correlation to how much the patients could relate to the visualization of their lost limb. Furthermore, the study showed that phantom limb pain patients with a telescoped phantom, i.e. the feeling that the phantom has retracted towards the stump, did not have an effect of the treatment. This research points to a possible connection between body perception, cortical reorganizations, and pain.

Inline with these results, this PhD thesis concerns a series of three studies investigating how cortical plastic changes and pain processing are affected by changing the body perception through the manipulation of visual feedback. Through this PhD work, a novel platform based on augmented reality was developed to study the above factors. The initial study concerned the development of the augmented reality system for the remaining studies. The system was tested on a sample of healthy participants and was found adequate for use in experimentation. The second study investigated how perceptions of the body changed when participants experienced a loss of visual input that resemble a limb amputation. This was achieved through the use of the augmented reality system developed through the initial study. Healthy volunteers participated in the study, and psychophysical, behavioral and electroencephalographic measurements were included. The results of this study showed that a loss of visual input created sensations reminiscent of phantom limb phenomenon in healthy volunteers and changes in cortical activity to stimulation were also observed. The third and final study used the augmented reality platform to create and perform an intervention for phantom limb patients experiencing telescoped phantoms. Using the augmented reality system, a personalized virtual visualization of the amputee's phantom was used to match the individually perceived deformations of the limbs, in an attempt to increase relatedness to the visualization. The final study includes behavioral and fMRI measurements, before and after treatment, to assess cortical changes. The findings of this study showed a significant reduction in pain over the sessions and indications of reorganization of the somatosensory areas.

The results point to an important role of visual feedback in maintaining a coherent body perception, both in healthy people and in phantom limb patients.

Dansk resumé

Fantomsmerter er en af smertevidenskabens store gåder. Trods anseelige mængder af studier og den jævne forekomst af fænomenet, er det stadig uklart hvad der er årsag til at nogle amputerede udvikler fantomsmerter. I de senste to årtier, har en af de førende toerier været, at der efter en amputation sker plastiske ændringer i hjernen, der fører til fantomsmerterne. Det er dog stadig et spørgsmål om disse plastiske ændringer er kausale, eller en affødt effekt af phantomsmerterne. Flere terapiformer er blevet opfundet baseret på denne teori, og én af dem er spejlterapien, hvori fantomsmertepatienter kan se en visuel genskabbelse af deres manglende kropsdel. Formålet med denne terapi er at genskabe sensorisk feedback fra kropsdelen, der derved genaktiverer de neural kredsløb der normalt behandler indtryk fra og omkring kropsdelen. Genaktiveringen af de neurale kredsløb tilbagefører de plastiske ændringer i hjernen og nedbringer derved smerterne, ifølge teorien. For nyligt viste et studie at effekten af spejlterapi har et sammenfald med hvor meget den enkelte patient kan relatere til den genskabte visualisering af kropsdelen. Derudover viste studiet at patienter der havde et teleskoperet fantom, hvilket betyder at deres fantom føles kortere end den amputerede kropsdel, ikke havde nogen effekt af terapien. Dette studie, og tidligere forskning, peger på et sammenfald mellem fantomsmerter, plastiske ændringer i hjernen og kropsopfattelse, udtrykt ved teleskopering af fantomet.

Denne PhD-afhandling omhandler en fortsættelse af denne forskning, og indeholder konkret tre studier, hvor sammenfaldet mellem plastiske ændringer i hjernen og smerte påvirkes ved at manipulere visuel feedback. Det første studie omhandlede udvikling af et augmented reality system, der blev anvendt i de to efterfølgende studier. Det udviklede system blev afprøvet på en gruppe raske forsøgsdeltagere og den tilhørende software er derudover blevet lagt åbent ud, så det kan anvendes af andre forskere indenfor perceptionsforskning. Det næste studie anvendte det udviklede system til at fjerne visuel feedback fra armen af forsøgsdeltagere, så det skabte et visuelt udtryk der lignede en amputation af forsøgsdeltagernes arm. Raske forsøsgdeltagere deltog i studiet og blev målt med physkofysiske, behavoristiske og elk-

troencefalografiske mål. Studiet viste at fornemmelsen af armen ændrede sig og på nogle punkter var sammenlignelige med nogle af de fornemmelser fantomsmertepatienter oplever. Derudover var der ændringer i de elektroencefalografiske målinger, der tyder på at hjernen processerer stimuli fra armen anderledes, når visuel feedback er fjernet. Det tredje og endelige studie undersøgte ændringer som følge af at lade fantomsmertepatienter anvende og træne med en viualisering af deres manglende arm, der var individuelt justeret til deres opfattelse af armen, samt kunne styres ved hjælp af muskler i den tilbageværende del af armen. Studiet anvendte funktionel hjerneskanning til at detektere ændringer i hjernen som følge af træningen. Resultaterne viste en signifikant forbedring i smerteniveauet, ændringer i kropsopfattelse, samt indikationer på hjerneændringer som følge af at anvende systemet over en to-ugers periode. Samlet peger forskningen på at koherent kropsopfattelse og visuel feedback har væsentlig betydning for såvel fantomsmertepatienter som raske individer.

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Abbreviations

ACC Anterior Cingulate Cortex. 18

AoV Angle of View. 23, 25, 26

AR Augmented Reality. ix, x, 2, 21, 22, 24, 25, 27–29, 33, 45–47, 55

BOI Body Ownership Illusion. 32, 33

CNS Central Nervous System. 4

CRPS Chronic Regional Pain Syndrome. 10, 14

EBA Extrastriate Body Area. 12, 13, 31

EEG Electroencephalography. 31, 40

EMG Electromyography. 24, 25, 27, 28, 30, 47, 49, 50

ERP Event Related Potential. 31, 40–43

fMRI Functional Magnetic Resonance Imagining. 18, 31, 48, 52

HMD Head Mounted Display. 18, 22–27, 29, 30, 33, 46, 47

ICA Independent Component Analysis. 42

IPL Inferior Parietal Lobule. 11, 13, 15, 17, 18, 41, 43

IPS Intraparietal Sulcus. 17

M Mean. 28, 29, 41, 52

MD Mean Difference. 37, 40, 49, 50

MEG Magnetoencephalography. 32

MPI Multidimensional Pain Inventory. 48, 50

MR Mixed Reality. ix, 22, 33–36, 38, 39, 55

NRS Numerical Rating Scale. 37, 48, 51

PCG Post Central Gyrus. 13, 32

PFC Prefrontal Cortex. 18

PLP Phantom Limb Pain. ix, x, 2–7, 9–11, 14, 21, 24, 45–49, 52, 53, 55–57

PME Phantom Motor Execution. 6

PMv ventral Premotor Cortex. 13

PPC Posterior Parietal Cortex. 12–14, 18, 41, 52

RHI Rubber Hand Illusion. 16, 17, 28–30, 32, 33, 39, 49, 52

RM-ANOVA Repeated Measures Analysis of Variance. 40, 41

rTPJ right Temporoparietal Junction. 13, 14

SD Standard Deviation. 28, 29, 37, 40, 41, 52

SEM Standard Error of the Mean. 29, 30, 51

SI Primary Somatosensory Cortex. 2, 13, 14, 18, 31, 41, 52–56

SII Secondary Somatosensory Cortex. 13, 14, 18

SPL Superior Parietal Lobule. 13, 17, 18, 41, 43

TMS Transcranial Magnetic Stimulation. 13

VAS Visual Analogue Scale. 41, 42, 49, 50, 55

VR Virtual Reality. x, 21, 22, 25, 28–30, 46, 47

Preface

The work that you are about to read is the culmination of 3 years work at the Center for Neuroplasticity and Pain (CNAP) at Aalborg University. My initial interest for this Ph.D. was sparked when I heard of an opening position wherein a new augmented reality system had to be created in order to visualize missing limbs for amputee patients. The idea was to recreate the lost sensory feedback for these patients in order to alleviate phantom limb pain.

This was intriguing, as I previously have worked within virtual reality and augmented reality. This meant that I had the expertise and know-how to realize this new augmented reality system. While I had a strong background knowledge on the technical aspects of developing such a system, a new challenge for me was understanding the pathology of phantom limb pain and how it could be studied and mended.

In the initial sections I will clarify the goal of this thesis, as well as introduce the problem of phantom limb pain and the current research on the topic. The second chapter will concern a more general introduction to the field of manipulating bodily perception through the use of visual manipulation and how it potentially can influence pain. The third chapter will introduce the development of a augmented reality system which serves as the foundation of the proceeding research. The same chapter will end with a presentation of the findings of a study on healthy participants, where the effects of losing own-limb visual feedback was investigated. The fourth chapter takes the previously presented topics and discuss these in relation to phantom limb pain and presents the results obtained in an experimental intervention using the augmented reality system on amputees with phantom limb pain. Finally, a synthesis is presented on the impact of the present work and how it applies to current phantom limb pain research.

Mikkel Thøgersen
Aalborg University, January 2, 2019

Chapter 1

Introduction

Phantom limbs are a well-known and well-studied phenomenon, however, despite efforts and a great number of studies, its aetiology is still unclear. Phantom limbs can occur when a body part is removed or missing from the body. It mostly occurs in amputees, but cases of congenital amputees describing phantom limb experiences have been reported as well (Ramachandran and Hirstein, 1998; Kooijman et al., 2000).

Almost all amputees feel a phantom in the time following their amputation (Jensen et al., 1983; Hanley et al., 2009). For some, the phantom disappears again after a period of time (from years to decades) and for some it persists (Kooijman et al., 2000). While the sensation of having a "ghost" limb may be unsettling, about half of amputees perceives additional feelings, such as a change in the shape and that the phantom limb is deformed in some way. For example, the phantom is often felt as retracted towards the residual limb, a phenomenon known as *telescoping* (Guéniot, 1861). Telescoping is seen in about half of upper-limb amputees and in one third of lower limb amputees (Mitchell, 1872). An array of other deformations, ranging from anatomically implausible configuration to shrinking are also common. In addition to deformations, about 50-80% of amputees experience pain in their phantom of varying degrees (Kooijman et al., 2000). These sensations are often described as a painful numbness, burning pain or they can have distinct physical qualities such as nails endlessly cutting into the palm (Ramachandran and Hirstein, 1998; Mitchell, 1872; Henderson and Smyth, 1948). Such sensations can be debilitating to the patient and have consequences for social life, ability to work and a decrease in quality of life.

Current treatments for phantom limb pain separate into two categories: pharmacological and stimulation strategies. Pharmacological treatments rely on anticonvulsants, analgesics and drugs targeting neuropathic pain, and have limited effectiveness (Flor, 2002; Bæk Hansen et al., 2018). Stimulation strategies range from sensory stimulations of the stump (Flor et al., 2001a) and mirror visual feedback training (Ramachandran and Rogers-Ramachandran, 1996) to transcutaneous electrical nerve stimulation (TENS) (Katz and Melzack, 1991; Tilak et al., 2016).

Mirror visual feedback training has been the topic of several promising studies (Chan et al., 2007a; Foell et al., 2014; Finn et al., 2017). This method works by recreating visual feedback of the lost limb by mirroring the intact limb over to the contralateral side. Despite knowing how the mirror works and that their limb *is* missing, most amputees sense a very real relation to the mirror image. Even healthy participants can experience this odd sensation. From this curious type of treatment, several new interventions have been invented based on this principle (Murray et al., 2007; Cole et al., 2009; Trojan et al., 2014; Ortiz-Catalan et al., 2016). Despite the promising results of the mirror visual feedback training, there is, however, no clear answer to what drives pain relief from this kind of treatment. Is it a memory of an intact limb that is "woken" through the recreation of the visual aesthetics of the limb? Is it due to a visual congruence to the perceived? Or is it an adherence to an innate perception of a prototypical bodily layout?

1.1 Aim and purpose of the present dissertation

The aim of this project was to use visual feedback as a tool to investigate mechanisms of pain-related plasticity and the possibility to reverse plastic changes using motor-facilitated visual feedback training in an Augmented Reality (AR) environment.

AR allows novel visual manipulations of own-body visual feedback which enables novel experimental paradigms to explore the relationships between pain, somatic sensations, pain-related plasticity and body perceptions. Pain and cross-modal perception is assessed using psychophysical and neuropsychological methods. Brain related changes and plasticity are monitored using EEG and fMRI.

The project addresses the following research questions:

1. Is it possible to alter experimental pain and body perception in healthy individuals by manipulating bodily visual feedback?

2. Does cross-modal integration influence the organization/reorganization of the sensory cortices (i.e. Primary Somatosensory Cortex (SI))?

3. Is it possible to create pain relief in Phantom Limb Pain (PLP) patients by restoring visual feedback of the limb and recreating volitional control?

These questions were addressed in three studies:

1. Thøgersen M., Graven-Nielsen T., Petrini L. OpenARRP: An Open Augmented Reality Research Platform for behavioral neuroscience and perception research. *Transactions on Applied Perception*, Under review.
2. Thøgersen M., Hansen J., Arendt-Nielsen L., Flor H., Petrini L. Removing own-limb visual input using mixed reality (MR) produces a "telescoping" illusion in healthy individuals. *Behavioural Brain Research*, 347: 263-271, 2018.
3. Thøgersen M., Andoh J., Milde C., Graven-Nielsen .T, Flor H., Petrini L. Effects of individually-optimized augmented-reality training on phantom pain and cortical reorganization following amputation. *Pain*, under preparation.

The coming section contains a brief overview of the current theories on the pathogenesis and aetiology of PLP.

1.2 Current theoretical framework on PLP

Phantom limbs are inherently difficult to explain due to the heterogeneity of the phenomenon and consequently there are an array of explanations, research and theories. Likewise, there are specific theories for the origin of the associated pain. As noted by Henderson and Smyth (1948), phantom limbs and phantom limb pain may be reflections of the natural functioning of the nervous system and could be a way to study the fundamentals of the system itself, lending further reason to study the phenomenon. Below are current theories and factors that are being investigated in relation to phantom limb pain.

1.2.1 Non-cortical origins of PLP

The neuroma and the peripheral origin

Amputation results in axotomized nerves that sprout and form a neuroma. The neuroma is a bundle of free nerve endings, that often exhibit increased sensitivity towards stimuli and abnormal ectopic discharges (Wall and Gutnick, 1974). The ectopic discharges are believed to provide the ongoing painful sensations in phantom limb pain and possibly the phantom phenomenon itself. Patients with total and partial section of the spinal cord, can however also experience phantom pain, which is the main counterargument for a peripheral origin of phantom pain (Melzack, 1990). A recent study by Vaso et al. (2014) showed that an injection of a local anaesthetic into or near the surface to the dorsal root ganglion corresponding to the axotomized nerve, resulted in an abolishment of PLP and even phantom perception, arguing for a peripheral origin.

1.2.2 Cortical basis of phantom limb pain

Memories of pain

It has been noted by several authors (Mitchell, 1872; Henderson and Smyth, 1948; Katz and Melzack, 1990; Flor et al., 2006) that the pain experienced by many amputees with PLP is a distinct pain that can be traced back to some specific pre-amputation pain. This observation led Katz and Melzack (1990) to propose a theory based on these descriptions by the patients. According to the theory, the experience of a pre-amputation pain of sufficient intensity is imprinted in the neural structures and will, at a later stage, result in the association of this pain to the phantom. However, this is confuted by the evidence of PLP in patients that did not experience pain before the amputation (Hanley et al., 2009).

Neuromatrix

Melzack (1990) proposed a pragmatic theory to explain phantom limbs and the associated pain based, primarily, on a set of observations from PLP patients. The theory was not limited to PLP, but rather described a general framework for understanding body perception, pain and somatic sensations. Instead of considering single stimuli reaching distinct areas of the cortex, the idea was to consider the *pattern* of signals constantly bombarding the Central Nervous System (CNS). These would appear in a "neural signature" in the "neuromatrix" of processing loops in the cortex. This pattern, or neural signature would result in the immediate experience of the body and when abnormal activity occur, such as from ectopic discharges from the periphery or central sensitization in the spinal cord, the absence of the ongoing regular activity would result in the experience of the sensory qualities associated to the phantom. The theory is hardly testable and should be viewed as a framework rather than an operational theory that can predict certain outcomes. As such, it does not present an immediate solution to PLP, but encourages a holistic approach to chronic pain where cognitive, affective and sensory factors are of equal importance to maintain a normal neural signature (Melzack, 2001).

Maladaptive plasticity and cortical reorganization

During the nineties evidence for cortical reorganization as the basis of phantoms and phantom limb pain emerged from a series of studies on macaque monkeys and human amputees (Elbert et al., 1994; Flor et al., 1995; Pons et al., 1991). Although, there were several suggestions of similar mechanisms in the past (Mitchell, 1872; Katz, 1921; Henderson and Smyth, 1948), these new studies provided the initial direct evidence to support a cortical origin of phantom limb pain. In the study by Flor et al. (1995) a strong correlation was discovered between phantom limb pain intensity and the amount of reorganization in S1. This resulted in the idea that cortical reorganization could be closely connected to PLP. These findings rely on correlations, hence, causation still remains to be established.

Flor et al. (1995) proposed that when an afferent input to the cortical areas previously responding to limb activity ceased to send signals, an adaptive process occurs to recover functionality. In the amputees where PLP occurs, this process may have become maladaptive and associated to the maintenance of pain. The maladaptive plastic changes proposed here, may have origin in changes in lower level structures, for instance in the thalamocortical projections to S1, though the authors state that these would not be able to explain the relatively large reorganizations observed. It should be stressed that the idea of reorganization is proposed as a probable result of low-level processes.

Preserved function model

Makin et al. (2013) presented findings of an fMRI study comparing PLP patients with congenital amputees without phantoms and healthy participants. They found that phantom movements generated activation in the original hand area of S1, and that the magnitude of this activity was highly correlated to the amount of chronic PLP. Furthermore, the same measure was significantly different from the activity elicited in healthy participants but not from congenital amputees when imagining similar movements. In addition, gray matter volume was found to be reduced in phantom patients compared to congenital amputees and healthy participants. This reduction in gray matter volume was also correlated to the amount of phantom pain, such that more pain was associated to preserved gray matter volume.

When the authors attempted to measure individual cortical reorganization using a classic measure from several previous studies on phantom limbs, they failed to find a significant relationship, as previously reported by others (Flor et al., 1995; Birbaumer et al., 1997; Lotze et al., 2001; MacIver et al., 2008). They did, however, criticize the methods applied in these previous studies for being imprecise. Instead, they correlated the activity in the area corresponding to the phantom hand movements, and showed that greater activity was significantly associated with greater pain.

These findings led to the hypothesis that chronic phantom pain is actually associated to conserved function in the organization of the limb in S1, whereas sensory deprivation, i.e. in the case of congenital amputees, is associated to less preserved function.

Sensory incongruence as a cause of PLP

Harris (1999) suggested that PLP was a result of conflicting motor intention and sensory feedback. Similar to how incongruence between vision and the vestibular system can generate nausea, he predicted that an incongruence center in the cortex would generate pain when motor intention did not match with afferent sensory feedback. Harris (1999) went on to propose that it might be the cause of other chronic pain states as well, e.g. the limited visual and proprioceptive feedback from the lower back might give rise to some forms of low-back pain.

Stochastic Entanglement

Ortiz-Catalan (2018) proposed a new hypothesis named *Stochastic Entanglement* in the attempt to explain PLP. The hypothesis states that after deafferentation or sensory deprivation, the neural circuitry involved in processing of input from the body part will enter a certain state of perturbation. In this state, the area is susceptible to "wire" to nearby areas through stochastic processes, i.e. random processes, possibly resulting in a wiring to the networks associated with pain perception and thus giving rise to PLP. According to Ortiz-Catalan (2018) this can explain why some amputees develop PLP immediately upon amputation, and some develop it only later, if at all. It also explains the cortical reorganizations that occur and the observed connection to the amount of PLP, as well as referred sensations from, e.g. the cheek, in some amputees.

An important point of the hypothesis, is the ability to "reverse" these randomly generated connections through the inverse of Hebbian learning, i.e. instead of "neurons that fire together, wire together", "neurons that fire apart, wire apart". With this, Ortiz-Catalan (2018) propose that recreating activity in the sensory and motor circuitry of the deafferented or sensory deprived body part, will make the circuitry "fire apart" from the surrounding cortical regions, and consequently, this will make them "wire apart".

The hypothesis, as such, borrows many ideas from the maladaptive plasticity theory of Flor et al. (1995), but manages to formalize it into some testable hypotheses. The proposed method of reversing the cortical reorganization is through Phantom Motor Execution (PME), which the author has spearheaded for the past years (Ortiz-Catalan et al., 2014a,b, 2016). Finally, Ortiz-Catalan (2018) dismisses the idea that visual feedback should be important for treatment.

This brief overview of the current theories conclude the introduction and will help to position the current work into the research field. The following chapter concern the interplay between visual feedback, body perception and pain. This will lead to how these factors can be manipulated to investigate own-limb visual feedback in healthy individuals and PLP in amputees with telescoping. Finally, the work will end with a conclusion and discussion of the overall findings and impact of the present thesis.

Chapter 2

Vision, pain and the link to body representations

Since Ramachandran and Rogers-Ramachandran (1996) popularized the use of mirrors in recreating the visual feedback of lost limbs, visual feedback has been a recurrent treatment modality for PLP. Vision, by itself, has been shown to be the dominant sense in multiple studies (Rock and Victor, 1964; Ernst and Banks, 2002) and can alter pain response when viewing the site of experimentally induced pain (Longo et al., 2009; Cole et al., 2009; Diers et al., 2013; Romano et al., 2016). In the field of PLP research, numerous studies have used vision as the main modality to generate pain relief (Ramachandran and Rogers-Ramachandran, 1996; Moseley, 2004; Carrino et al., 2014; Murray et al., 2007; Cole et al., 2009; Mercier and Sirigu, 2009; Finn et al., 2017) to name a few. For a review, see (Dunn et al., 2017). The treatment, however, has also found its use in several other areas, such as in treatment of CRPS and rehabilitation of stroke patients (Rothgangel et al., 2011).

Moseley and Flor (2012) reviewed approaches to treat chronic pain, such as PLP, by targeting cortical representations. In their review, different modalities of sensory stimuli where discussed, including visual feedback as a potentially viable method to reduce chronic pain by provoking cortical reorganizations. However, they argued that sensory stimuli alone is not sufficient to provoke cortical reorganizations, these must be functionally relevant and salient to have the desired effects (Moseley and Flor, 2012). The notion that sensory stimuli can generate cortical reorganization is supported by the observed expansion of the cortical representation of hands in highly specialized hand-work individuals, such as in string instrument musicians (Elbert et al., 1995).

In PLP research, Chan et al. (2007b) ran a controlled trial with a crossover design on mirror therapy. They asked amputees with PLP to perform mirror movements with the intact limb and the phantom limb, while observing the mirror reflection. As control conditions, another group was asked to perform the same movements, but using a mirror covered with an opaque sheet of cloth and a third group was told to do mental visualization of the movements. A significant decrease in pain was found from the mirror therapy during the initial randomized trial. Likewise, during the crossover period, a significant decrease in pain was observed for the two control groups. Whereas the study of Chan et al. (2007b) was performed on lower-limb amputees, Finn et al. (2017) repeated the same study in upper-limb amputees and found similar effects. These two studies indicate that neither mental effort nor actual motor effort are sufficient to obtain decrease in pain. But the addition of visual feedback, i.e. functionally relevant stimuli, was needed for the effects to occur.

Likewise in Chronic Regional Pain Syndrome (CRPS) patients, Moseley et al. (2008b) showed that functional relevance was similarly necessary to achieve a decrease in pain. The study involved CRPS patients in a within-subjects, repeated measures design, where tactile stimuli was applied during two phases. During one phase, stimuli was applied while patients were occupied by either reading a magazine or listening to music, while in the experimental phase, they were asked to discriminate between the stimuli by location (on an image of the affected area) and size of the device used for stimulation. The results suggested that there was a clear pain relief obtained when discrimination was performed, but not in the control condition. Additionally, Flor et al. (2001b) showed that a discrimination-based approach, using electrical stimuli, resulted in significant pain reductions in amputees with PLP.

Thus, functional relevance seems to be paramount in generating pain relief. The reason for this importance of functional relevance is scarcely the focus of current research. When amputees with PLP perform bilateral movements of both the intact and phantom limb, it will generate activity in some areas, e.g. pre-, supplementary- and motor cortices, thalamus, and the somatosensory cortex from the resulting afferent feedback. However, when adding functionally relevant stimuli, such as visual feedback in mirror therapy, a new set of areas and cognitive processes will activate based on this stimuli. These processes, it seems, are likely a determining factor in generating a decrease in pain. Likewise, in CRPS patients, stimuli alone did not impart pain decrease, but adding functional relevance to the stimuli seemed to induce an effect.

In the case of visual feedback for amputees with PLP, a study by Foell et al. (2014) suggested that the amount of pain relief obtained from mirror therapy was associated to the sense of agency ("the feeling that leads us to attribute an action to ourselves" (Foell et al., 2014; Farrer et al., 2003)) over the mirror image. This was supported by results of a questionnaire, where the amputees reported how much they could relate the movement they saw in the mirror to their own phantom. The result of this question was closely correlated to the amount of pain decrease obtained from the mirror therapy. Additionally, they observed a correlation of pain relief to cortical activity in the Inferior Parietal Lobule (IPL), which is thought to be involved in the sense of agency (Farrer et al., 2003). Furthermore, pain relief was not obtained in those PLP patients whom experienced telescoping. The authors therefore discussed that treatment effect possibly could be determined by the amount of "relatedness" to the mirror visual feedback, i.e. if a patient experiences a telescoped phantom, but sees the mirror image of the intact and fully extended limb, it may be difficult to "relate" to the mirror image. This "relatedness" is associated to body ownership, a general feeling that our body belongs to us, and in this case, that the limb in the mirror belongs to the amputee. The ability to have ownership and feel agency over the visualization could be the cognitive counterpart to the neural processes that bring about the decrease in pain observed in mirror therapy for PLP patients (Foell et al., 2014; Chan et al., 2007a; Finn et al., 2017). To explore this further, the following section presents an overview of these and related concepts.

2.1 Our body in the brain

In the process of relating visual feedback to ourselves, it is necessary to be aware of how our body is arranged and that our body belongs to us, which can be referred to as "body awareness" (Berlucchi and Aglioti, 2010). The following concepts attempt to capture the mechanisms involved in this process.

2.1.1 Body schema and body image

Body schema and body image have been a dynamic duo, defined and redefined several times in literature and are often confused. They are attempts at dissociating two concepts that convey information about the body. The latest definition of the two concepts was developed by Gallagher (2005) with the effort to clarify the confusion of the dichotomy adopted in previous research. Gallagher clarifies how these concepts constitute the sense of one's own body and how it is used as an explanatory concept which shapes perception in a body-centric space.

Body schema is defined as *"a system of sensory-motor capacities that function without awareness or the necessity of perceptual monitoring"* (Gallagher, 2005), and it is related to motor capacities, abilities and habits.

Body image is a conscious perception of having a body. It can be referred to intentions directed at or concerning to one's own body.

According to Gallagher (2005), *"The difference between body image and body schema is like the difference between a perception (or conscious monitoring) of movement and the actual accomplishment of movement, respectively."* (Gallagher, 2005). The two concepts are based on empirical evidence of double dissociation in neurology. For example, disorders that lead to a loss of large myelinated fibers produce a loss of proprioception and tactile feedback. Patients suffering from such disorders were investigated by Cole and Paillard (1995) who found that these patients were unable to sense their body postures and consequently had to rely on visual feedback to guide their body movements. These individuals had impaired body schemas, whereas awareness of the body image was intact. Unilateral neglect patients, on the other hand, lose awareness of one side of the body and are examples of the opposite, i.e. impairment of the body image.

Gallagher (2005) noted that while these two concepts have been useful as operationalizations, their use have been confused and incorrect in several academic works. Berlucchi and Aglioti (2010) discuss these problems and conclude that the vague definitions of body image and body schema make them ineffective. Instead, Berlucchi and Aglioti (2010) argues that these concepts should be abandoned, and focus should be on the many newly identified areas and networks that relate to the functions associated to body image and body schema that combined constitute body awareness.

2.1.2 Cortical body representations

The difficulties in defining neural correlates of body awareness are apparent from the word "awareness". Awareness is undeniably connected to consciousness and the neural correlates of consciousness are unclear at best. However, some areas have been identified to activate on certain sub-tasks that likely subserve our understanding of body awareness.

To limit the scope of this discussion, the discussed areas will be reduced to those that are likely relevant to this work, furthermore, the thalamocortical connections that exist in all these areas are not mentioned for the sake of avoiding repetitions (Andersen, 2011). These cortical areas include, but are not limited to:

The Extrastriate Body Area (EBA) is located in the dorsal visual stream and selectively activates upon vision of body parts, but may also activate on self-generated movements (David et al., 2007; van Koningsbruggen et al., 2013). Saxe et al. (2006) found that it activates selectively on allocentric body parts, i.e. body parts arranged in such a way, that they could not be one's own, questioning whether the area is self-other discriminative too, though this is not certain (Hodzic et al., 2009).

Posterior Parietal Cortex (PPC) is intricately involved in body perception, as is apparent from literature (Ehrsson, 2005; Tsakiris, 2010; Berlucchi and Aglioti, 2010; Longo et al., 2012). It is believed to have a significant role in localizing the limbs in 3D space, which is supported by single neuron recordings in monkeys (Sakata et al., 1973). Experimental data in human participants suggests that the limb position is determined in network between the PPC, EBA and the ventral Premotor Cortex (PMv) (Limanowski and Blankenburg, 2016).

Inferior Parietal Lobule (IPL) constitutes the inferior part of the PPC. It contains a relatively large number of bimodal neurons, that receive input from extrastriate visual areas, in the dorsal visual stream, as well as input from SI (Andersen, 2011). Together with the Superior Parietal Lobule (SPL) it is believed to be instrumental to a "where" system, i.e. the localization of objects (Andersen, 2011), and is likely to exhibit some component of self-other distinction in agency (Farrer et al., 2003).

Right Temporoparietal Junction (rTPJ) refers to the area of the angular and supramarginal gyra and has been found to be involved in the sense of ownership. Studies applying electrical stimulation to the site, have been able to induce out-of-body experiences repeatedly (Blanke et al., 2002), while lesions in the area have shown to impart autotopagnosia (Berlucchi and Aglioti, 2010). Tsakiris et al. (2008) conducted a study using Transcranial Magnetic Stimulation (TMS) over the area, while inducing an ownership illusion. They found that the disruption of the rTPJ resulted in a reduction in a measure of ownership, indicating that the area has an important function in assigning ownership.

Post Central Gyrus (PCG) contains the Primary Somatosensory Cortex (SI) which costitutes the anterior bank of the PCG. Experiments point to that, despite the commonly believed static nature of the somatotopy, it seems to react more to the current perception, rather than a one-to-one correspondence (Schaefer et al., 2007, 2009, 2013). The PCG is connected to various other areas, such as Secondary Somatosensory Cortex (SII) and IPL. Tsakiris (2010) argues that the PCG, together with the somatosensory associative cortex, located in the (SPL), contains an "online" postural and anatomical representation of the body.

Insula is believed to be involved in consciousness, interoception and homeostasis. Due to the deep location of the structure and its involvement in body awareness functions (Farrer and Frith, 2002; Farrer et al., 2003), some authors argue that it could be a possible origin of a prototypical body layout (Moseley et al., 2012b).

The areas briefly presented above are all essential to normal functioning. Lesion studies show that damage to one of these can result in impairment of complex functions, such as agnosia (loss of ability to recognize various objects) to somatoparaphrenia (loss of ownership of a body part or a whole side). A well-known example of these deficits is neglect syndromes, where one hemisphere or a certain body part is neglected, or the awareness of one side of the visual field is impaired. These are typically associated to damage to the PPC (Bear et al., 2001). Evidence from focal brain lesions of the parietal area in PLP patients, have shown complete abolishment of their phantoms (Ramachandran and Hirstein, 1998), arguing for the heavy involvement of this area in phantoms and PLP.

Moseley et al. (2012b) proposed a "body matrix" composed of many of the previously mentioned areas, that work in symphony to account for the integrity of the body at the psychological levels and in adaptation to changes in orientation and structure. The authors touch on the possibility that the body matrix could be involved in generating beneficial effects in chronic pain conditions, such as CRPS and PLP. This suggestion is mostly supported by the observed reorganization in SI following amputation and in CRPS patients, which would link it to their body matrix.

Another model specifically for body-ownership, was proposed by Tsakiris (2010). The model, likely inspired by models of agency (David et al., 2008), is based on a set of comparators to determine the whether an entity belongs to the body. An initial comparison is made between anatomical properties of the body and the incoming sensory information, in particular, the visual impression. This is believed to take place in the rTPJ. In a second comparison, the postural and body state, i.e. the physical configuration, is compared in SI and SII. Finally a comparison is made between the somatic senses and the previous correspondence in the PPC. The sensation of ownership over the body part, or entity, is envisioned to arise as a function of activity in the right posterior insula (Tsakiris, 2010).

2.1.3 Agency and Ownership

Agency (the perception of having volitional control over a body part) and body ownership (the feeling that our limbs are part of our own body) are intertwined sensations that influence one-another. Despite this, the two sensations have been discerned in recent studies and literature (Tsakiris et al., 2007; Gallagher, 2005).

Clinical examples of the two distinct concepts are somatoparaphrenia, a delusion in which a patient denies ownership over one of the patients own limbs (Moseley et al., 2012b) and alien hand syndrome, in which a patient loses control, but also agency over a limb (Assal et al., 2007).

Agency

Agency can be described as the recognition that you are the agent initializing and performing an action (Gallagher and Gallagher, 2000). Literature on agency argues for at least two levels of agency: *pre-reflective agency*, i.e. agency at a lower level, which is usually not consciously processed and *judged agency*, where a agency is judged based on a conscious reflection (Gallagher and Gallagher, 2000). The pre-reflective, low-level agency also referred to as the "sense of agency", have been commonly explained using the *comparator model*, a model where a set of comparators assess intended action with perceived action to determine if there is congruence between these (David et al., 2008).

When an intention to perform an action is created, a new intended state of the body is created. This desired state is compared to the current, dynamically updated state to create a set of motor commands necessary to achieve the desired state. The motor commands are issued both to the periphery *and* as an internal *efference copy*. From the periphery, a barrage of sensory feedback concerning the motions performed will integrate to form a new estimated state of the body. Using an internal body-model, the efference copy is interpreted into a predicted body state. Finally, the estimated and predicted states are compared and the difference between these states results in an error signal, that signifies match or mismatch and subsequently the sense of agency (David et al., 2008). Synofzik et al. (2008) corrected the comparator model from being a single system to consist of a range of agency-related cues that integrate in a Bayesian manner to generate a unified sense of agency. The comparator model is believed to act subconsciously, but if incongruence is sufficiently salient, then the incongruence may provoke conscious perception (Synofzik et al., 2008).

Judged agency can be referred to as the "feeling of agency". The distinction is made based on the observation that in everyday life, we do not consciously process the sense of agency. When we start to notice agency, it becomes subject to a conscious judgment of agency.

Farrer et al. (2003) attempted to detect the neural correlates of the sense of agency by using positron emission tomography in an elegant experimental task. Participants were asked to control a joystick while viewing a, seemingly collocated, virtual version of the same joystick. When participants moved the joystick, they would see either a congruent movement or offset movements (by 25° and 50°). By analyzing the data according to the increasing degree of incongruence, they found that the activity in the IPL increased and the activity in the right posterior insula decreased. Both of these areas are known to be involved in several high-level body-related functions, as previously discussed (in subsection 2.1.2).

Ownership

Similar to agency, ownership (also referred to as body ownership) suffers from the inherent difficulty in both defining and assessing it (Gallagher, 2005). Gallagher and Gallagher (2000) defines ownership as: "The sense that I am the one who is undergoing an experience" (Gallagher and Gallagher, 2000). As with agency, ownership has at least two levels, the pre-reflective and judged ownership (de Vignemont, 2011). Furthermore, ownership is often attributed by the sense of agency, as the sense of agency includes a component of self-other discrimination (Farrer and Frith, 2002), thus ownership may be even more elusive as compared to agency.

The topic of ownership, as a separate phenomenon, became the interest of much research through the discovery of the Rubber Hand Illusion (RHI) (Botvinick and Cohen, 1998; Ehrsson et al., 2004; Ehrsson, 2005; Tsakiris and Haggard, 2005; Kalckert and Ehrsson, 2014; Fuchs et al., 2016; Martini, 2016) (to name a few, for a review see (Kilteni et al., 2015)). The RHI is an illusion wherein a participant feels that a rubber hand is his/her own hand (ownership). The illusion is generated through a visuotactile stimulation. The visuotactile stimulation consists of concurrent and coherent visual and tactile stimuli of both the rubber and the participants' hidden real hand, which convinces the mind of the percept that the visualized, i.e. the rubber hand, corresponds to the corporeal (Botvinick and Cohen, 1998).

Judged ownership over the rubber hand has been measured using several different questionnaires in literature (Botvinick and Cohen, 1998; Longo et al., 2008; Ehrsson et al., 2004; Kalckert and Ehrsson, 2012; Bekrater-Bodmann et al., 2014). To measure pre-reflective ownership is inherently more difficult, however, throughout the literature, a measure based on proprioception has been used as an indirect measure of this ownership. Participants of the RHI (and other similar approaches (Thøgersen et al., 2018; Schmalzl and Ehrsson, 2011; Schmalzl, 2011)) are asked to indicate the position of their hidden real hand before the RHI, by sliding their finger on a ruler on a transverse axis in front of their body (usually on a plane corresponding to the location of their hidden real hand). Following, the illusion is created using the visuo-tactile stimulation, and participants are asked once again to perform the measurement. If the illusion is effective, then it is possible to observe a shift or a proprioceptive drift from the real hidden hand towards the rubber hand. Although most literature does not discern between judged and pre-reflective ownership, it seems that proprioception is likely a measure of pre-reflective ownership (Kammers et al., 2011; Kalckert and Ehrsson, 2012; Tsakiris et al., 2006). Rohde et al. (2011) and de Vignemont (2011) did, however, point out that this is a problematic association, as it is only an assumption that it measures pre-reflective ownership.

In an fMRI study on the RHI, Ehrsson et al. (2004) found that activity in the bilateral premotor cortices was significantly correlated with ownership, measured with a questionnaire. In addition, the study showed activity in the Intraparietal Sulcus (IPS), which is the sulcus separating the IPL and SPL. This area is functionally connected to both visual, somatosensory and premotor areas and thus is an area involved in the multi-sensory integration (Ehrsson et al., 2004).

Due to the fact that agency and ownership are intertwined in nature, another conglomerate concept was added to the rubber hand illusion, namely, *embodiment* (Giummarra et al., 2007; Longo et al., 2008).

2.1.4 Embodiment

Embodiment can be described as "the bodily self-consciousness", "sense-of-self" or "corporeal awareness". It is a conglomerate term including the two sub-components, agency, ownership as discussed previously, plus a third *location* component which covers the bodily layout that makes us able to sense the location of our body (Longo et al., 2008). The identification of these three components is based on a psychometric decomposition of subjective reports, developed by Longo et al. (2008).

Agency, ownership, location and the conglomerate embodiment can all be manipulated using the RHI, according to the various measures used throughout the different studies (for reviews see (Giummarra et al., 2008; Kilteni et al., 2015)). Recently, experiments using visual manipulation to alter embodiment-related sensations have shown that not only do these manipulations affect these sense-of-self related variables, but they can even change the perception of experimentally induced pain.

2.2 Vision and embodiment as tools to manipulate pain

In the introduction to this chapter, a range of studies were discussed which all indicated that vision and embodiment can influence pain processing in individuals with chronic pain. The following will outline studies that argue for similar effects on pain processing in healthy individuals.

Longo et al. (2009) showed that nonspecific visual feedback of the hand, versus a neutral object and another person's hand could reduce experimentally induced pain and change cortical processing, as measured using laser-evoked potentials. Later, it was shown that altering the visual size of a stimulated hand could also affect pain processing, such that an increase in visual hand size led to a reduction in pain, as measured using thermal threshold testing, and vice versa for visual size reduction (Mancini et al., 2011).

In a further extension of the findings of the study of Longo et al. (2009), Hänsel et al. (2011) showed that vision of a corporeal as compared to a non-corporeal object could similarly increase the pain threshold for experimentally induced pain. They used a camera filming the back of a mannequin or a cardboard box and fed the video to a Head Mounted Display (HMD) worn by the participant. Either object and the participant was stroked synchronously or asynchronously to generate an *out-of-body-illusion* and induce ownership or self-identification with the carboard box or the mannequin (Lenggenhager et al., 2007). They found that self-identification with a human-shaped object, i.e. the mannequin, was significantly increased over the cardboard box and generated a heightened pain threshold. Furthermore, the relationship between the degree of self-identification and increased pressure pain thresholds correlated significantly. Expanding on these results, Diers et al. (2013) showed that this analgesic effect is also present for pressure pain thresholds both in healthy participants and in patients with low back pain.

Longo et al. (2012) continued the study of the analgesic effect of viewing one's own hand by repeating the study with Functional Magnetic Resonance Imagining (fMRI)-recordings, providing neuroimaging correlates of the analgesic effect. Participants received nociceptive laser stimuli under two conditions, either watching a wooden box or watching their own hand, while recording fMRI. They found a widespread network of areas that activated differently, including: the occipital areas, IPL, SPL, Prefrontal Cortex (PFC) and others, which the authors refer to as the "visual body matrix" (this was proposed approximately concomitantly with the "body matrix" by Moseley et al. (2012b)). Additionally, activity in SI resulting from the stimulation was reduced when viewing the hand as opposed to an object. Using the PPC as a seed region, a psychophysiological interaction analysis was conducted, which showed that viewing the hand resulted in an increase in functional coupling between PPC, SI, SII, Anterior Cingulate Cortex (ACC) and the anterior and posterior insula. This advocates for the involvement of these areas in recognizing the visual feedback as the own hand.

For the present work, a highly interesting study was done by Martini et al. (2014) who showed that similar analgesic effects, as those found by Longo et al. (2009), can be transferred into virtual reality. A key result of this study was that while vision of a virtual arm did not induce a significant increase in heat pain thresholds over control conditions, viewing a virtual arm *that felt like your own* induced a significant increase in heat pain thresholds. This indicates that an embodiment of the virtual arm did create an analgesic effect, implying the importance of sense-of-self for altering pain processing. In the study, the authors used a finger tracker, which could transfer the movements of the real finger onto the virtual avatar in the virtual environment to induce embodiment. It should be noted that they included an asynchronous condition, in which the finger moved asynchronously with the participants' movements, and while this condition did have a higher pain threshold than control conditions, it did not reach significance, whereas the synchronous condition did (Martini et al., 2014).

Several of the mentioned studies in this section speculate that the degree to which these effects of visual feedback are expressed are related to the ownership, agency and embodiment over the respective visualizations, thereby relating these perceptual and neural processes to the processing of pain (Longo et al., 2009; Hänsel et al., 2011; Moseley et al., 2012a; Foell et al., 2014). Thus, vision and embodiment, it seems, are powerful tools if they can be manipulated.

Chapter 3

Manipulating visual feedback in the healthy individual

From the previous chapter we learned that vision can be a powerful tool in affecting pain perception. The challenge is to manipulate it efficiently, which this chapter will address together with a discussion on own-limb visual feedback in general. The first section will review current methods to manipulate visual feedback within perception and PLP research, and give an overview of the current state-of-the-art within this topic in section 3.1. This will include a taxonomy for categorizing the visual manipulation systems based on their intrinsic features in subsection 3.1.1. To address some of the shortcomings of previous approaches to visual manipulation, a novel AR system was developed and tested through Study I, and it is presented in subsection 3.1.2 and 3.1.3. Next, own-limb visual feedback and how it can influence neural processing is discussed in section 3.2, and finally, the developed system from Study I was used in Study IIA & B, to investigate the impact of *removing* own-limb visual feedback in subsection 3.2.2 and 3.2.3.

3.1 Modalities of visual manipulation

A number of devices and contraptions have been used to manipulate vision, from mirrors (Ramachandran and Rogers-Ramachandran, 1996), to rubber hands (Botvinick and Cohen, 1998; Schaefer et al., 2007), Virtual Reality (VR) (Cole et al., 2009) and lately AR (Trojan et al., 2014; Ortiz-Catalan et al., 2016). The recent development and availability of consumer VR have allowed researchers to use this tool in their experimental research (Bohil et al., 2011; Slater et al., 2009; Martini, 2016).

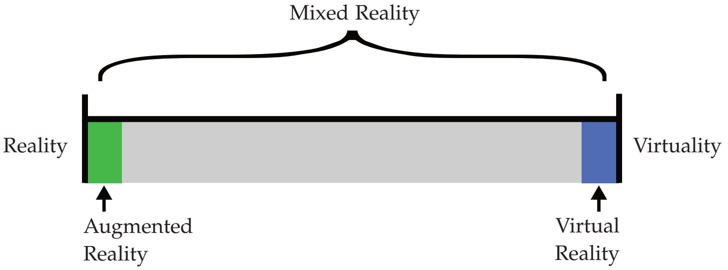


Fig. 3.1: Depiction of the Reality-Virtuality continuum. The continuum refers to *experiences* rather than devices, however, devices are often limited to a certain range of experiences on the axis. The left end represents reality, as we see it, the green is where AR devices are. To the right is virtuality, where everything is computer-generated and virtual, the blue portion depicts where VR is located. The grey area in between is where MR devices are located. (After interpretation of figure originally presented by Milgram et al. (1994))

VR refers to technologies that can immerse a user into a virtual, computer-generated environment. There are several technologies to achieve immersion in virtual environments. The most common method is through the use of HMDs, which consists of screens positioned in front of each eye of the wearer. This technology allows for complete control of visual input to a subject, which makes it a convenient tool in experimental research. The more advanced technology, AR, refers to superimposing virtual content onto imagery of the real world in real-time. This can be achieved in several ways, for example by filming a scene and augmenting the video-feed, in real-time, with virtual, computer-generated content. Recently, optical see-through displays have been invented that allow normal vision, but with the possibility to add virtual content. VR and AR are located near the two extremes on an axis known as the reality-virtuality continuum. A third category, Mixed Reality (MR), refers to the *mixes* in between, but also includes both VR and AR, see figure 3.1.

For the present work, one of the research goals was to manipulate bodily visual feedback and study whether it can affect pain perception and body perception. Thus, to investigate this, a system allowing for visual manipulation was needed. To make the visual manipulations convincing for the wearer, the system needed to convey real vision which could be manipulated, i.e. an AR device. Therefore, the following review of existing methods, will be limited to AR systems. Different types of AR devices exist and they can be stratified based on their intrinsic features.

3.1.1 A taxonomy of MR devices

Milgram et al. (1994) developed a taxonomy to classify MR systems as a continuum from entirely real environments over AR to VR and virtual envi-

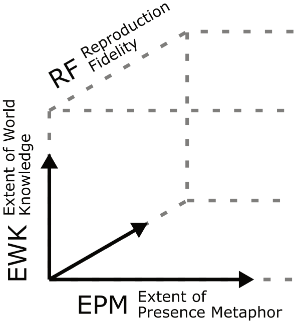


Fig. 3.2: Depiction of the three axis of used in the taxonomy proposed by Milgram et al. (1994). Milgram et al. (1994) notes that, despite the depiction, the axes are not entirely perpendicular, as EPM and RF both meet at the extreme where systems displaying virtual and real vision are indistinguishable from each other. (After interpretation of figure originally presented by Milgram et al. (1994))

ronments (see figure 3.1). A sub-classification of this was proposed, which consists of three dimensions on which systems can be localized and compared. A depiction of this three axis model is shown in figure 3.2. The dimensions are:

- Extent of Presence Metaphor (EPM), a measure of how present the system allows the user to be. At one end, it has a static image on a monitor and at the other it has real-time video in an HMD.
- Extent of World Knowledge (EWK), where, as the name suggests, the system is rated according to the degree to which it "knows" about the real world environment. A monitor would be at the one end, whereas a tracked HMD would have some sensor "telling" it where it is located, and thus a higher extent of world knowledge. This factor may seem unintuitive initially, but it is paramount in modelling the virtual elements and environments, e.g. measure the orientation of an HMD to move a virtual environment according to the motion of the head.
- Reproduction Fidelity (RF) describes how well the system can convey its visual impressions to the user, which often translates into screen resolutions and Angle of View (AoV). This factor stretches from monoscopic, monochrome, low resolution displays to high definition, high dynamic range, color-accurate, real-time stereoscopic displays.

Within this taxonomy, egocentric or allocentric viewpoints are among the most important distinctions. The former is a system where the viewpoint coincides with the user's eyes, whereas the latter is a system where the viewpoint does not coincide with the user's eyes. Another relevant intrinsic feature is stereoscopic versus monoscopic vision. Monoscopic refers to a system that is using a single image, whereas stereoscopic refers to a system that delivers stereovision. Allocentric systems typically use two separate images, i.e. one image for each eye, which can create a sense of depth (Aukstakalnis, 2016). Recently, optical see-through systems have become available on the consumer market, they use a transparent display in front of the eyes, enabling the real visual input to reach the eyes, but with the possibility of adding virtual elements. These should be viewed as different to video-feedback systems, where cameras film the scene and transport it to some monitor or screen with virtual elements added.

Only few studies have used AR in PLP research, three examples are listed below together with a short note on their intrinsic features and their relative positions within the taxonomy outlined by Milgram et al. (1994).
A monoscopic, allocentric, video-feedback system was used in the recent study by (Ortiz-Catalan et al., 2014b, 2016). It used a camera situated on top of a monitor to film the user. The image was then displayed on the monitor with an added virtual phantom, creating a mirror-like effect. The EPM factor of this system is in mid to high range as it is monitor-based, but does convey the sense of being present by imitating a mirror using real-time video feedback. The EWK is fair, as in this system, the relative position of the display device and the object of interest, the residual limb, is tracked using a marker. Furthermore, the arm is modelled using Electromyography (EMG) signals from the residual muscles. Finally, the RF is in the low end, due to the fact that it is an allocentric system, i.e. the reference viewpoint does not coincide entirely with the user.

Trojan et al. (2014) used a video-feedback system as a form of mirror visual feedback system. It used two cameras attached to an HMD, streaming the footage into the screens of the HMD. This system has a markedly higher degree of EPM than the previous, as it is real-time, stereoscopic and egocentric. Likewise it would be rated higher in RF factor, due to the same reasons. Finally, EWK would be comparable to the previous system as it used computer vision to track the position of the hands and fingers.

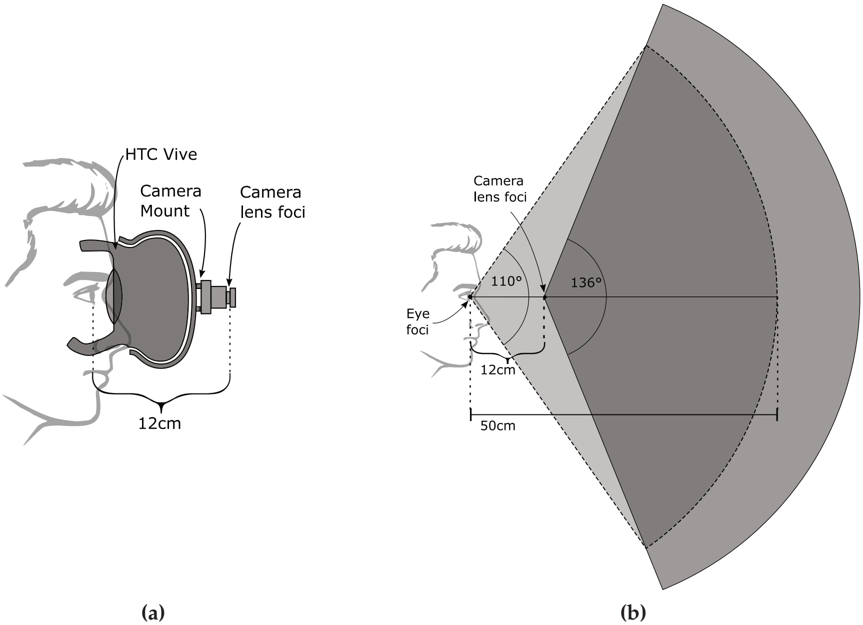
An interesting mixed modality system was used by Penelle et al. (2012), wherein a 3D camera filmed the user and projected a 3D image of the user on a screen. By using a set of stereoscopic glasses they could create a sense of depth. It falls between most of the categories in the taxonomy, as it is neither purely stereoscopic or monoscopic, nor allocentric or egocentric. Using the taxonomy of Milgram et al. (1994), the EWK would be superior to the previous two systems, as the 3D camera effectively models the entire view. On the EPM-factor it would be in the high end, as it uses real-time imaging and simulates stereoscopic view. RF on the other hand, is limited, as the resolution of the used sensor is poor.

Optical see-through systems have not been used in phantom limb research yet. Compared to video-feedback systems, optical see-through systems are able convey real, undelayed, vision while adding virtual content. This has the advantage that nausea is reduced greatly due to the complete synchrony between visual impressions and sense of balance. Furthermore, the currently available systems "map" their environment by constantly 3D-scanning it. This enables them to place virtual content in relation to real-world objects, which could be beneficial for, e.g. placing a virtual phantom visualization in extension of the residual limb of an amputee. However, there are caveats to the current available optical see-through devices, such as semi-transparent virtual elements and reduced active AoV (the area that can display virtual elements). The current systems have about one-tenth of the active AoV of competing VR systems (comparing the Microsoft HoloLens (Kreylos, 2015) to the HTC Vive (Anthes et al., 2016)).

3.1.2 A novel AR system

In Study I, a novel AR device was created, which was able to manipulate vision sufficiently to investigate the research questions set forth in the conception of this work. The developed system consisted of a virtual reality HMD (HTC Vive, HTC Corporation, Taiwan), with two high-speed (58 frames per second), high-definition (2056 by 1542 resolution) cameras attached to the front, which streamed the video-feeds into the monitors, similar to the system of Trojan et al. (2014). When using cameras for video see-through, an inherit problem is that the cameras cannot be co-located with the eyes and therefore has an offset perspective. To accommodate this problem, the lenses of the cameras were chosen to match the AoV of the HMD, and consequently the human eye, at the approximate eye-to-hand coordination distance of 50 cm. This was chosen as a compromise to keep perspective at this distance as close to regular vision as possible. A depiction of the camera arrangement on the HMD is shown in figure 3.3.

This video-see-through system allowed for adding virtual content to the view, making it an AR system. Because the system was based on the HTC Vive platform, which provide accurate tracking of both the system and a set of peripherals (Islam et al., 2016), it was able to track the position of a peripheral attached to the limb of the user (HTC Vive Tracker, HTC Corporation, Taiwan). Furthermore, by adding an eight channel EMG measuring armband (Myo armband, Thalmic Labs, Canada), the intended movements could be decoded, as in the system used by Ortiz-Catalan et al. (2014b). Successively, this system was used to superimpose a virtual arm to the users arm, which in the case of amputees would be a visualization of their phantom limb. The features of the developed system meant that the system would be ranked superior to previous systems in almost all factors of the taxonomy proposed by (Milgram et al., 1994). Particularly, these features are: 1) the



(a) (b)

Fig. 3.3: (a) shows a section through the HMD, with lens, camera mount and camera. The distance from camera foci to eye foci is approximately 12 cm. (b) Shows the AoV comparisons between the Vive view, the used lens offset of 12 cm with a matching AoV at 50 cm distance from the eyes of the wearer (an estimate of hand to eye distance).

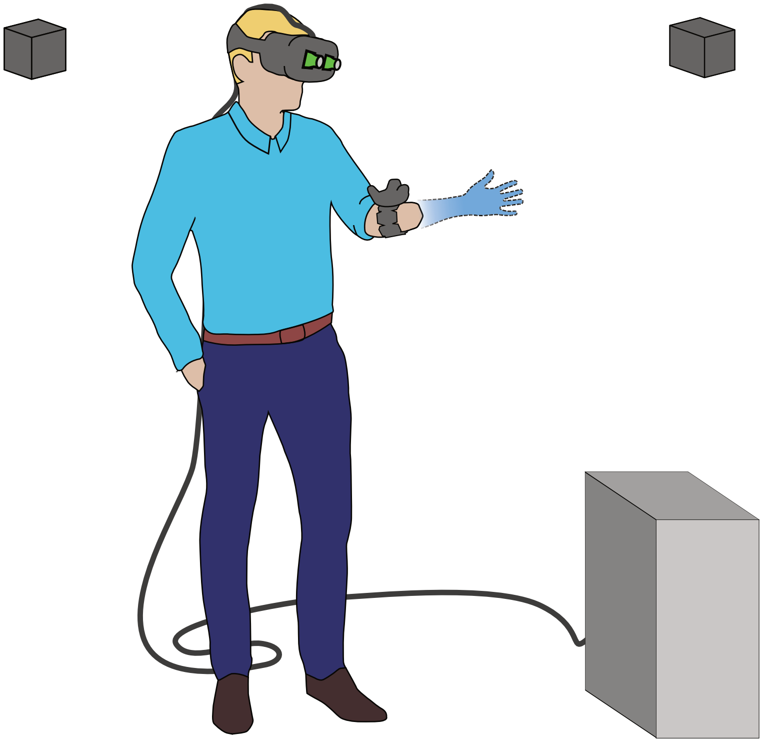


Fig. 3.4: Overview of the AR platform developed in Study I, depicted for the use case of a phantom visualization on an amputee. In the top corners, the two boxes depict lasers that are used for tracking the HTC Vive system. The user is wearing the HMD with the two cameras attached to it. From the HMD, a cable bundle transfers the camera images to the computer and sends the finished AR images back to the screens in the HMD. On the patients' right arm are depictions of the EMG measuring armband and the position tracker. These devices transfer EMG, position and orientation data to the computer wirelessly, to track the muscle contractions and movements of the residual limb. In extension of the residual limb, the visually recreated limb is depicted in blue with dashed lines.

egocentric, stereoscopic vision, which makes the system rank equally to the system proposed by Trojan et al. (2014) on the EPM factor, 2) the stereoscopic, high definition cameras and screens would rank the system superior to previous systems on the RF factor, but still inferior to an optical see-through system, 3) the relative tracking of limb and HMD position would grant it a higher rating than the previous systems on the EWK factor. A depiction of the system developed through Study I, as it would be used for amputees, is shown in figure 3.4.

3.1.3 Study I - Validating the usability of the custom built AR system

Study I - Validation design The aim of this study was to obtain measures of certain qualities of the system. Healthy participants with perfect or corrected to perfect vision were asked to test the system for 15 minutes doing five minutes of three interactive tasks using a virtually overlaid arm, controlled through the EMG armband. These tasks consisted of: a sorting task, where items had to be sorted into correct bins; a pick and place game, where objects had to be picked up and placed accurately on another spot, and finally; an imitation game, where subjects had to mimic movements of a virtual "ghost" arm, using their overlaid arm. Example views of these tasks are shown later in chapter 4, figure 4.2.

Study I - Methods To test how well the system could display virtual content and video from the cameras on the front, the subjects were initially tested for visual acuity in the system using a Snellen chart test (Snellen, 1862). This test measures sight relative to perfect vision, to obtain a ratio of visual acuity as compared to perfect vision. Next, to control the virtual arm, the EMG data had to be interpreted by a machine learning algorithm. To calibrate the algorithm, the participants were asked to perform a set of movements. The algorithm was based on non-negative matrix factorization and was implemented based on the study by Jiang et al. (2009a, 2013). Following the calibration, participants tested the system for 15 minutes and provided scores on questionnaires reflecting their experience. The questionnaires assessed: 1) the sense of presence (Witmer et al., 2005); 2) the sense of agency, ownership, location (a measure of how co-located the participant felt) and embodiment of the virtual arm, which was assessed using a questionnaire originally intended for the measuring these aspects in the RHI (Longo et al., 2008), consequently, there were few changes of wording in the questionnaire; and finally 3) simulator sickness (Kennedy et al., 1993), which measures the extent of physical reactions to motion sickness.

Study I - Results Ten subjects (N = 10) were recruited through personal inquiry at Aalborg University and all completed the study. Results of the Snellen chart test showed that visual acuity for virtual content and video see-through content were equivalent (VR: Mean (M) = 20/103.80, Standard Deviation (SD) = 8.63 feet, AR: M = 20/99.80, SD = 10.04 feet) [1]. The presence questionnaire results are shown in figure 3.5, alongside presence questionnaire scores for a VR system and a C6 CAVE system[2] (Miller et al., 2017).

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[1] Snellen charts measure the relative visual acuity to a person with perfect vision in terms of *distance*. For example a person with 20/80 vision at 20 feet away can see what a person with perfect vision can see at 80 feet away, i.e. one-fourth the visual acuity based on distance.

[2] A Cave Automatic Virtual Environment (CAVE) system is usually a room with projectors displaying a virtual environment on the walls, ceiling and floor. These systems often create an

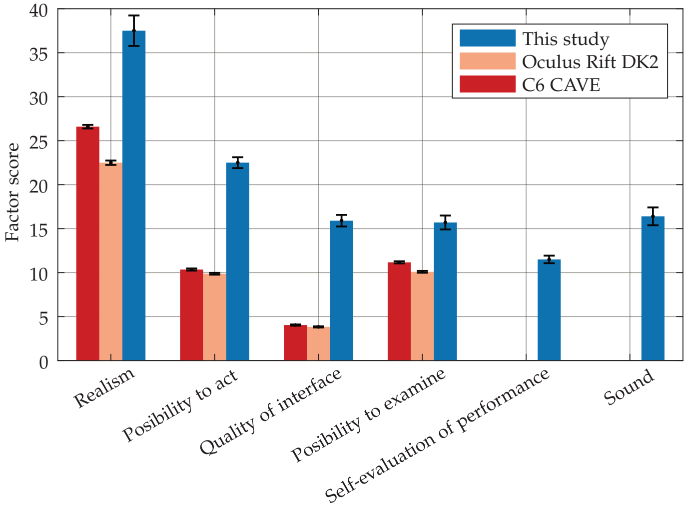

Fig. 3.5: Factor scores in the presence questionnaire compared to the Oculus Rift DK2 VR system and the C6 CAVE system (Miller et al., 2017). Greater scores in the individual factors are better. Whiskers correspond to the Standard Error of the Mean (SEM).

Study:	This study	Oculus Rift[a]	Google Cardboard[a]	3D TV[a]	TH-57 simulator[b]	SL1 simulator[c]
Total:	20.20 ± 16.18	26.64 ± 7.19	17.29 ± 7.02	17.11 ± 6.27	9.80 ± 15.00	14.00 ± 11.33

Table 3.1: Simulator sickness scores (M ± SD) for the developed system and: (a) roller coaster simulation in an Oculus Rift, Google Cardboard and a 3D TV (Chessa et al., 2016); (b) Military helicopter simulator with force simulation through a motion base (Kennedy et al., 1993); and (c) A car simulator, also with force simulation (Balk et al., 2013). Note greater scores mean more sickness, i.e. lower scores are better.

Simulator sickness questionnaire scores are summarized in table 3.1 together with simulator sickness scores from other comparable systems (Chessa et al., 2016; Kennedy et al., 1993; Balk et al., 2013). Results from the RHI questionnaire are plotted in figure 3.6, together with the scores from a RHI study (Longo et al., 2008).

The Snellen chart tests indicated that the resolution of the cameras was able to take advantage of the full resolution of the HMD monitors, as both VR and AR content had similar visual acuity. Results of the presence questionnaire showed that there were a high sense of presence compared to other VR systems (Miller et al., 2017). The same was true for the scores of the RHI questionnaire, which were all better compared to the RHI. It should be noted that the RHI is concerned with a static rubber hand, whereas the

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egocentric viewpoint for a single user by tracking the location and position of the head.

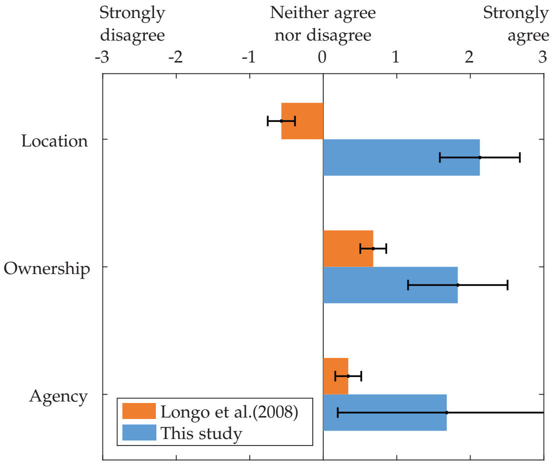

Fig. 3.6: Rubber Hand Illusion (RHI) questionnaire factor scores for the current study and those of the study by Longo et al. (2008) on the RHI. Greater scores correspond are better in this case. Whiskers represent the SEM.

virtual hand in this study is animated and controlled through the EMG armband, and thus, greater scores were expected. The simulator sickness questionnaire scores obtained were greater than those of simulators with motion base systems to simulate forces (Kennedy et al., 1993; Balk et al., 2013). This is likely due to an extended latency in the developed system, which was measured to be approximately one tenth of a second (maximum 127 ms). An increase in latency as compared to VR systems is inevitable in video-based see-through systems, because the images have to be captured by the cameras and transferred into the HMD. VR systems generate the images directly, and thus, do not suffer from such extended latencies.

In the following section, an overview of studies that have manipulated own-limb visual feedback will be provided and discussed. It should be noted here, that a plethora of studies have been conducted on manipulating visual feedback in relation to limb movement, these are, however, not the focus of the following section, as these studies include *motion*. The reason for excluding limb motion is that it generates sensory feedback that can influence processing of other stimuli. To limit the following section, it only includes studies that can be compared to the conditions of an amputee, i.e. without movement.

3.2 Own-limb visual feedback

In normal functioning individuals, vision is an essential sense for a range of tasks: for monitoring action and movements, to locate objects in our environment, deciphering bodily expressions of our peers, etc. In amputees, vision of the amputated limb is lost along with the limb, but if visual feedback is recreated, as is the case in the mirror box illusion, it seems to have profound impact. So what does vision mean in an intact system? In this section, the aim is to understand and discuss the importance of vision over own-limbs, and in particular what it means, if own-limb visual feedback is removed.

There are many inquiries that could be posed for what own-limb visual feedback means in the intact system. One question, that might be an important first step, is whether or not there is a difference between looking at an arm that is your own (i.e. located with an egocentric perspective) as compared to the arm of another person (i.e. an allocentric, non-egocentric perspective). Saxe et al. (2006) performed an experiment to investigate this question. Participants were asked to watch allocentricly or egocentricly positioned body parts, while fMRI was measured. Their results indicated that the right EBA, dorsal prefrontal cortex and the post central gyrus were activated differently depending on the perspective. The right EBA was activated on allocentric perspectives, while dorsal prefrontal cortex and post central gyrus were activated during an egocentric view. The experiment relied on displaying images to the subjects and having them do a one-back task. The one-back task was used to ensure attention by having the subjects press a button if the current image was identical to the previous image (therefore the name "one-back"). Hence, the experiment relied on the visual feedback alone, showing that vision of an egocentric hand increases excitation of the SI and the other mentioned areas. Thus, vision of one's own body *is* discerned from the vision of others' bodies in neural responses.

The excitation of SI that occurs when a limb is observed in an egocentric reference frame indicates that the cortex processes vision of the body differently from other stimuli. But is this own-body specific processing reflected in multimodal sensory processing? This was tested in a study by Taylor-Clarke et al. (2002), using a combination of vision of the limb, tactile stimuli and Electroencephalography (EEG) to measure cortical Event Related Potentials (ERPs). Subjects were shown either their own arm or a cylinder that appeared to be co-located with their arm. Tactile stimuli were applied in a manner, such that the arm would disappear from 50 ms before delivering stimuli till 150 ms after delivering stimuli, ensuring that subjects could not see the actual stimuli. A similar timed auditory stimuli was used as a control stimuli. ERPs confirmed that SI activated differently from viewing the cylinder object with the same stimuli applied to the same arm. Additionally, viewing the arm increased the spatial acuity significantly and shows that own-limb vision has a profound impact on processing of stimuli in several aspects (Kennett et al., 2001). The ERPs of their study indicates that SI reacts indifferently to the immediate tactile afferent stimuli with or without vision of the arm (as concluded from the early N50-components, that have similar amplitude during both vision of own-arm and vision of the cylinder). At the later N80-component there were significant changes in amplitude between the teo visual conditions (Taylor-Clarke et al., 2002). Additionally, an auditory stimulation was given as a control stimuli and it showed that only tactile processing was affected by the visual condition (Taylor-Clarke et al., 2002). In their paper, Taylor-Clarke et al. (2002) discuss that the significantly different amplitude of the N80-component is likely associated to back-projections from multimodal areas located in the parietal cortex or the frontal areas.

Further evidence for the role of vision and the impact of multimodal areas on the processing in the PCG was shown in the study of the elongated arm illusion by Schaefer et al. (2007). In this study, the impression of an elongated arm and the concurrent processing of tactile stimuli was investigated. Schaefer et al. (2007) created this impression by having participants wear a sweater with one extended sleeve and a rubber hand at the end. The first and fifth digit on the hand were stimulated with a pneumatic device while measuring sensory evoked fields using Magnetoencephalography (MEG). When stimulating the hand while participants saw the elongated arm, a remarkable shift was observed in the site of processing in PCG. The activity for the two digits had moved significantly closer to one another than in the control conditions. The results shown in the paper of Schaefer et al. (2007) indicate and verify that PCG is indeed subject to modulation based on perception of body size and shape. Schaefer and colleagues have since demonstrated how PCG is dynamically modulated based on sensory perceptions (Schaefer et al., 2009, 2013).

Taken in summation, these studies show that body perception has a profound effect on neural processing, starting with mere vision of our own bodies and expanding through effects on somatic processing. The presented experiments rely on visual feedback of some object or body part, but in the case of amputees, the sense of the body part is present (i.e. the phantom), but no visual information is available in the phenomenal space of the sense of the missing limb. The following section will describe ways to recreate a similar experience in healthy participants, i.e. by removing co-located own-limb visual feedback, and thereby investigate the impact of missing own-limb visual feedback.

3.2.1 Removing own-limb visual feedback

Schmalzl and Ehrsson (2011) attempted recreate the visual feedback of an amputation in an experiment on healthy humans. They created this through the use of a full Body Ownership Illusion (BOI), an extreme form of the RHI, where another corporeal-like body is embodied using cross-modal induction. The authors used a set of cameras mounted on a mannequin to act as the *subjects' eyes*. The stream of video from these cameras were relayed to an

HMD mounted on the participant, letting her/him see the perspective of the mannequin. The cameras were tilted downwards to observe the body of the mannequin, which was missing the left hand. Hence, the subjects were observing the body of the mannequin, including the left arm with the missing hand, from an egocentric perspective. By performing synchronous brush strokes, as in the RHI, participants experienced an embodiment over the mannequin body. The synchronous brush strokes were performed in the empty space below the wrist and simultaneously on the wrist of the participant. The results indicated that participants felt the presence of their hand at the brushed locations and that the participants felt both an "invisible hand", like the phantoms of amputees, and a telescoping effect. This was reflected in a proprioceptive drift of the sense of the hand, measured by having the participants point with the non-illusory hand to the perceived location of the other illusory hand.

The intent of the study was to investigate whether a BOI could be used to induce ownership over an amputated body and, in that case, whether it would induce a telescoping sensation. While the study showed that both of these aims could be achieved, they were both achieved through induction of a BOI. Hence, the results reflect the malleability of the human body perception, but not what would happen if a healthy individual lost vision of their limb.

In an attempt to remove any mediating factors and investigate missing own-limb visual feedback directly, Study IIA & B used an early version of the developed AR system from Study I combined with *chroma-key composting*[3] to create a direct manipulation of the participants' own vision (Thøgersen et al., 2018). This combination could, thus, be used to create the visual aesthetic of an amputee, by realistically removing co-located, own-limb visual feedback. Furthermore, the combination of the AR system and chroma-key composting would change the classification to an MR system, rather than an AR system, due to its ability to selectively remove vision of real objects and make them seem invisible. Therefore, in this work, the application with chroma-key composting is referred to as the "MR system", whereas "AR system" refers to the system as it was applied in Study I.

3.2.2 Study IIA - Investigating the effects of missing own-limb visual feedback

Study IIA - Experimental design. To remove own-limb visual feedback, green chroma-key composting was used together with a green glove and sleeve. Participants wore the green glove and sleeve and were seated at a table with a dark tablecloth and the MR system fixated in front of their eyes.

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[3] Chroma-key composting, also known as green-screen, is known from weather forecasts and from movie production. It is a technique were all pixels of a certain colour in a video are replaced with another video or image.

Initially, they were asked to keep their hands outside the view of the cameras while a "background image" was captured. Now, with the background image captured, all the green coloured areas in the camera image could be replaced with the background image and it would seem as though the green areas were invisible. Hence, when participants were asked to put their hand with the green glove into the view of the cameras, it seemed invisible through the MR system. However, they were able to see the part of the arm that was not covered by the green fabric and thereby creating a "visual amputation". The method to achieve this is depicted in figure 3.7.

To assess the effects of missing visual feedback, Study IIA consisted of three different conditions: a condition without the MR system, i.e. normal vision (Baseline); a condition where the participants were looking through the MR system, but saw the unaltered video feed (Control), and lastly; a condition in which the MR system was used with missing visual feedback of the arm (no visual feedback). The no visual feedback condition was as follows; the "background" image was captured, then the participant placed their left hand, with the green glove, in the camera view while visual feedback was still present, subsequently a slow fading process was begun wherein the green color pixels were faded with the corresponding background pixels. While the fading happened, a short talk was read to the participant, to help maintain focus on the slowly fading hand. The talk consisted of statements like the following “I would like you to focus on your left hand. You start to notice how your hand slowly begins to disappear. . . disappears and becomes nothing..." Thøgersen et al. (2018). After the fading was completed, the hand had disappeared completely.

To assess the somatic senses of the "missing limb", a green screen was introduced covering most of the background and the hand. Subsequently the glove was removed from the subjects’ hand, which was now covered by the green screen. Subjects performed each of the no visual feedback and control conditions in a counterbalanced order. A depiction of this is shown in figure 3.8 and images from inside the system are shown in 3.9.

Study IIA - Methods. The aim of the study was to investigate the perceptual changes occurring when co-located visual feedback of the hand is removed. To detect these changes, proprioceptive localization of three landmarks on the hand was measured during each condition: the index fingertip, the knuckle and the wrist. This was conducted on a proximal-distal axis, and was effectuated using a slider mechanism underneath the table in front of the subject, i.e. the slider was not visible to the subject. For each landmark, the subject was asked to move the slider out to the location where he or she perceived the landmark to be on teh distal-proximal axis.

A custom questionnaire was used to asses the body perceptual changes following the no visual feedback and control condition. It consisted of 16

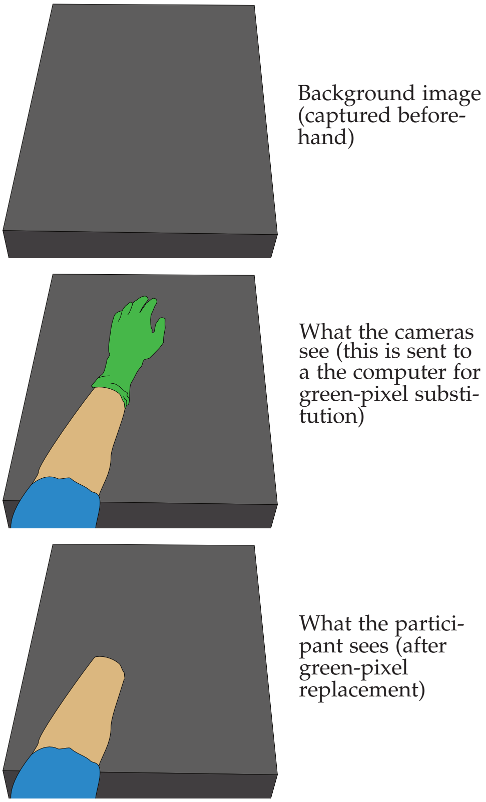


Fig. 3.7: Depiction of how the developed MR system can enable removal of selective visual feedback by the use of chroma-key composting. An image is captured of the scene without the object(s) from which visual feedback is unwanted (top image). Then, the object is introduced in the scene, but the unwanted part is covered with green (in this example a green glove, middle image). When the system is active, it then finds all green parts in the image and replaces it with the pre-captured image of the scene without the object - thus creating the appearance that the object is invisible (bottom image).

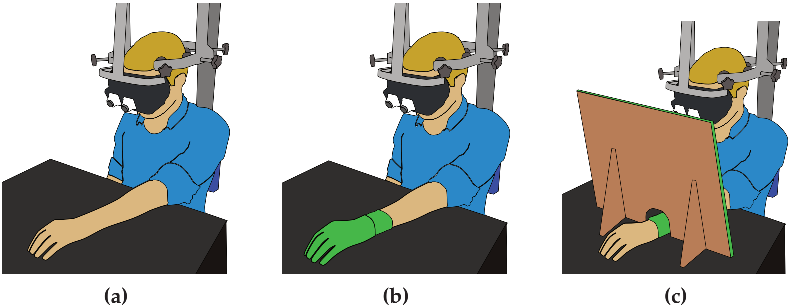

(a) (b) (c)

Fig. 3.8: Depictions of (a) control and (b and c) no visual feedback conditions of Study II. The baseline condition is not shown here. (a) Control condition: the hand was viewed through the MR system with no visual manipulation. (b) No visual feedback condition during the induction phase: the hand and glove was visible to begin with, but was slowly faded away using the background image. (c) No visual feedback condition when performing thermal threshold testing: when the hand had completely disappeared, a green screen was introduced, which appeared invisible to the participant. This often went unnoticed by the participants due to that all pixels of the green screen were substituted with background pixels. Subsequently the green glove was carefully removed, leaving the skin bare to assess somatic sensation, and the screen covering the testing area, i.e. all manipulation of the arm was invisible to the participant, who saw the arm and the static background image.

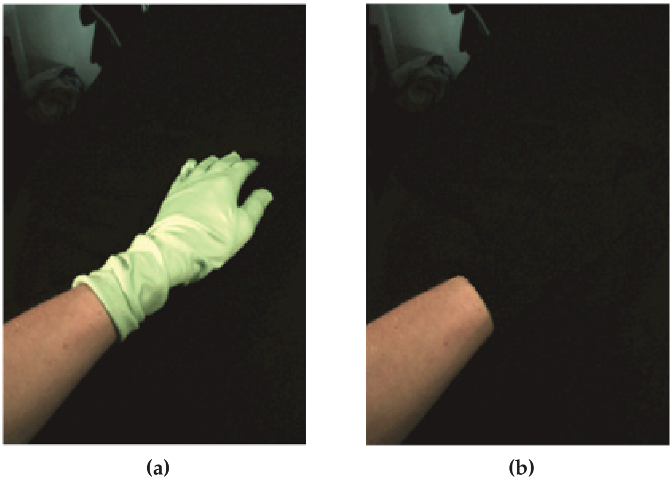

(a) (b)

Fig. 3.9: Sample images from the cameras of the MR system used in Study II. Image (a) shows the raw image of the camera, while (b) show the image after manipulation, i.e. replacement of the green colored glove in the image with the corresponding pixels from a pre-captured "background" image.

statements rated on a 7-point Likert Numerical Rating Scale (NRS) according to the subjects agreement to the statements (-3 = "I strongly disagree" to 3 = "I strongly agree"). Finally there were an interest to see whether thermal pain and detection thresholds would change, due to previously reported effects from body ownership manipulations and thermal thresholds testing (Osumi et al., 2014; Martini et al., 2014). Hence, a Peltier thermode (30×30 mm, Medoc Pathway, Medoc Ltd., Israel) was used in all conditions, to test thermal thresholds. These were ramped from 32 °C to 52.5 °C or 0 °C for heat stimuli and cold stimuli, respectively, at a rate of $1\,°\mathrm{C}\,\mathrm{s}^{-1}$. Subjects were asked to press a button when reaching the threshold in question, e.g. heat pain threshold, which would stop the stimulation and bring it back to 32 °C (Thøgersen et al., 2018).

Study IIA - Results. Subjects (N = 30, 15 female) for the study were recruited through personal inquiry at Aalborg University and all completed the study. The results of Study IIA showed that co-located loss of own-limb visual feedback induced a significant proprioceptive drift of the distal parts of the hand between control and illusion conditions (index finger tip: Mean Difference (MD) $= -3.65$, SD $= 3.03$, $t(29) = 6.59$, $p < 0.001$, index finger knuckle: MD $= -2.85$, SD $= 3.14$, $t(29) = 4.97$, $p < 0.001$ and, wrist: MD $= -2.06$, SD $= 3.28$, $t(29) = 3.28$, $p < 0.004$)(Thøgersen et al., 2018). These drifts are depicted in figure 3.10.

The thermal thresholds test results showed a significant effect of loss of visual feedback on cold detection thresholds (from control to no visual feedback condition: , which were lower compared to control (MD -0.55 °C, $p < 0.001$) and baseline conditions (MD -0.77 °C, $p < 0.001$), i.e. it took the patients longer to register the cooling of a Peltier-based thermode (Thøgersen et al., 2018). Cold pain thresholds and heat detection thresholds were shifted in both control and no visual feedback conditions, while there were no significant changes in heat pain thresholds.

Finally, questionnaires on the experiences of the no visual feedback indicated a dis-ownership of the hand ($p < 0.001$) and that subjects perceived their lower arm to be shorter than in the control condition ($p < 0.025$) and to have disappeared ($p < 0.050$). Furthermore, the responses indicate that subjects felt their hand to be lighter ($p < 0.040$) and a tickling or tingling sensation ($p < 0.025$), see figure 3.11.

These results showed that loss of vision, without any embodiment procedures, is enough to distort the body perception. The observed proprioceptive drift was larger at the distal parts, i.e. the finger tips, with gradually smaller effect of the drift on the knuckle and wrist. Vision, it seems, helps maintain a physically coherent proprioceptive layout of the hands and arms.

It has previously been shown that the senses integrate in a statistical opti-

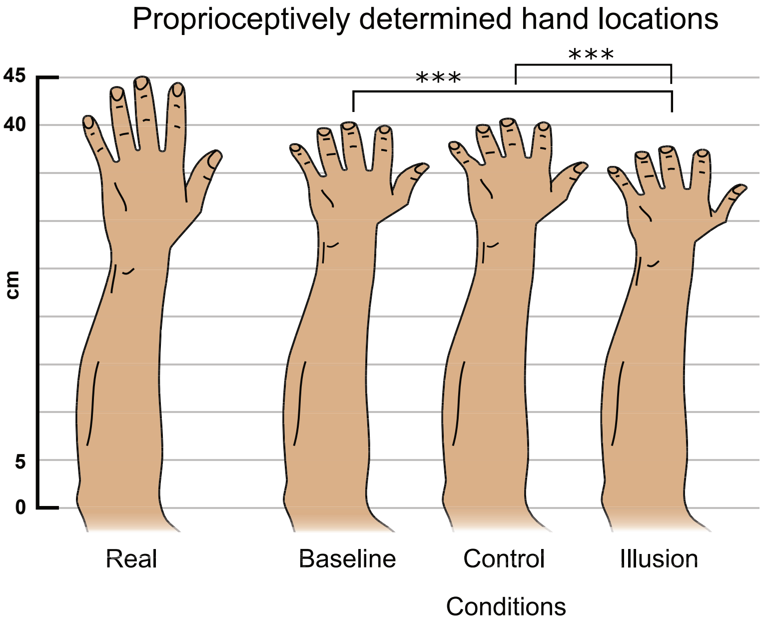


Fig. 3.10: The perceived proprioceptive layout during the different visual feedback conditions of Study IIA. The leftmost hand is a normal layout of a hand, continuing left, the hands correspond to: the average proprioceptive measures of the hand layout without any manipulation of the visual feedback (Baseline), the average measures of the hand with visual feedback through the MR system (Control), and finally the average proprioceptive measures following the no visual feedback condition. (*** = $p < 0.001$). Data for this graph was obtained in the study by Thøgersen et al. (2018).

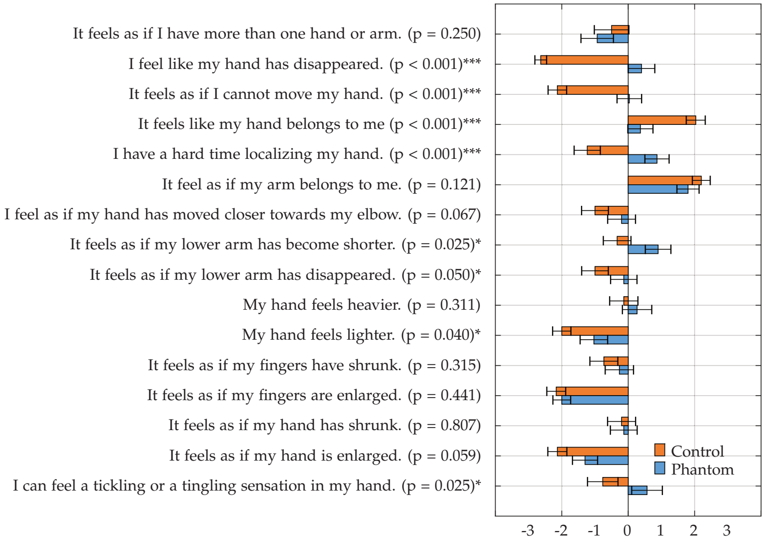


Fig. 3.11: Questionnaire administered following the control and no visual feedback conditions in Study IIA with the responses plotted in a bar diagram. Whiskers indicate the standard error of the mean. Wilcoxon signed ranks tests was used to compare the responses from the questionnaires (* = $p < 0.05$, *** = $p < 0.001$). Data for this graph was obtained in the study by Thøgersen et al. (2018).

mal fashion Ernst and Banks (2002); Synofzik et al. (2008) and many authors consider that there is an innate, or slowly adapting, representation of the body layout (cf. the body schema, as described by Gallagher (2005) or the offline representation discussed by Berlucchi and Aglioti (2010)). In the case of the proprioceptive drift observed in Study II, it could seem as though some skewed layout of the body is available to consciousness, but that this skewed layout needs correct afferent input to "normalize" it towards a physically correct layout. Removing vision of the hand, as done here, may have forced the internal layout to "normalize" towards the visualized, i.e. make the hand seem closer to the visual amputation.

The thermal threshold testing results indicate that cold detection alone is modulated by having no visual feedback, whereas the other threshold results indicate that vision through the MR system alone might influence their perception, i.e. not related to missing visual feedback. The finding that cold detection thresholds changed, could be related to a disownership of the manipulated hand, as disownership has been found to decrease the temperature of the real, disowned hand in a RHI study (Moseley et al., 2008a), however, that finding has not been replicated.

3.2.3 Study IIB - Neural correlates of somatosensory evoked potentials when missing own-limb visual feedback

Study IIB - Experimental design A similar experimental design as in Study IIA was used in a secondary pilot study, StudyIIB with 20 participants(in preparation). The aim of this study was to investigating the neural correlates of nociception when visual feedback of the stimulated limb was missing. Instead of a baseline condition, a condition where the hand was covered with a cloth, was added to the experimental study (covered condition). This condition was added to assess the difference between occlusion of visual feedback of the hand and co-located missing visual feedback. Each condition of Study IIB was separated into two blocks to avoid habituation to the electrical stimuli. For each stimulation intensity and condition, 30 trials were collected per subject.

Study IIB - Methods A concentric stimulation electrode was used together with EEG (G.Tec Medical Engineering GMBH, Austria) to record ERPs evoked by the electrical stimulation. A transcutaneous concentric electrode, introduced by Klein (2004) and modified by Lelic et al. (2012), was used to deliver electrical stimuli due to its ability to deliver a high current density, which results in selective activation of the superficial skin layer, where the Aδ nociceptors are located (Inui et al., 2002). This leads to an increased specificity in eliciting nociceptive stimuli at low stimulation intensities (Lelic et al., 2012). The electrode was placed on the forearm of the participant. Electrical stimuli were applied at two different intensities given in randomized order, the intensities were determined as: double the electrical stimulation detection threshold intensity (low intensity) and quadruple the detection threshold intensity (high intensity). 30 stimulation repetitions were acquired for each intensity and condition per subject. Subjects were asked to verbally report the pain they perceived after each stimulation, on a scale from 0 to 10 with 0 = "no pain", 5 = "moderate pain" and 10 = "unbearable pain". Proprioceptive drifts were measured using the same approach as in StudyIIA, additionally subjects were asked to estimate the location of the stimulation site in a similar manner, using proprioception.

Study IIB - Results The proprioceptive drift was increased in the covered condition compared to the control condition. While the covered and no visual feedback conditions had a significant difference from the control condition, there were no significant effect between covered and no visual feedback (finger tip: MD = 1.63 cm, SD = 4.43 cm, t(19) = 1.641, $p = 0.312$). Means and SDs are listed together with Repeated Measures Analysis of Variances (RM-ANOVAs) in table 3.2.

The pain scores from the stimuli were analyzed using a two-way RM-

Condition	Index finger tip	Knuckle	Wrist	Stimuli
Control	-4.2 ± 3.5	-0.7 ± 3.9	3.0 ± 4.2	0.4 ± 4.2
Covered	-6.2 ± 3.9	-2.3 ± 4.4	2.0 ± 4.5	-0.9 ± 4.7
No visual feedback	-7.8 ± 4.7	-3.2 ± 4.5	1.7 ± 4.5	-2.3 ± 5.5
RM-ANOVA	$F(2,38) = 9.409$	$F(2,38) = 3.820$	$F(2,38) = 1.082$	$F(2,38) = 4.706$
	$p < 0.001$	$p = 0.031$	$p = 0.347$	$p = 0.015$

Table 3.2: Proprioceptive drift results from StudyIIB. Values are given as mean ± SD in centimeters. RM-ANOVAs are reported in the bottom row.

Intensity	Control	Covered	No visual feedback
Low	1.38 ± 0.79	1.38 ± 0.84	1.30 ± 0.75
High	3.05 ± 1.35	2.88 ± 1.16	2.85 ± 1.36

Table 3.3: Pain ratings on a 10 cm Visual Analogue Scale (VAS) from electrical stimuli during each condition and intensity. Values are Ms and Standard Deviations (SDs) in the format: (M ± SD).

ANOVA with intensity and conditions as factors. The analysis showed no significant changes over conditions ($F(2,100) = 0.393, p = 0.676$), but significant differences between intensities ($F(1,100) = 150.881, p < 0.001$). No significant interaction was detected ($F(2,100) = 0.165, p = 0.848$). The means and SDs are shown in table 3.3.

The electrophysiological data showed significant differences when comparing the conditions located over the parietal area. Control and no-visual feedback showed considerable changes in activity over the parietal area, whereas changes between control and covered condition where limited to the visual cortex. When comparing the covered condition to the illusion condition, there were still significant effects located over the PPC and the visual cortex, see figure 3.12. A cluster-based permutation test was carried out on the grand mean averages of the individual electrodes to find significant differences in amplitudes. A significant increase in amplitude was detected in the no visual feedback condition, as compared to the control condition. The electrodes covering SI, SPL and IPL displayed significant differences at approximately 270-430 ms after stimulus, see figure 3.13. Differences between the control and covered condition where limited to two electrodes, the PO8 and Oz electrodes, and were observed between approximately 370-500 ms.

The topographies and ERPs show in concurrence that the neural processes are likely modulated by the missing visual feedback. The results also indicate that there are differences between occluding the view of the hand and removing co-located visual feedback. The intraparietal sulcus and IPL contain a large proportion of visuo-tactile bimodal cells that are involved in multisensory percepts (Duhamel et al., 1998) and includes a "where" portion

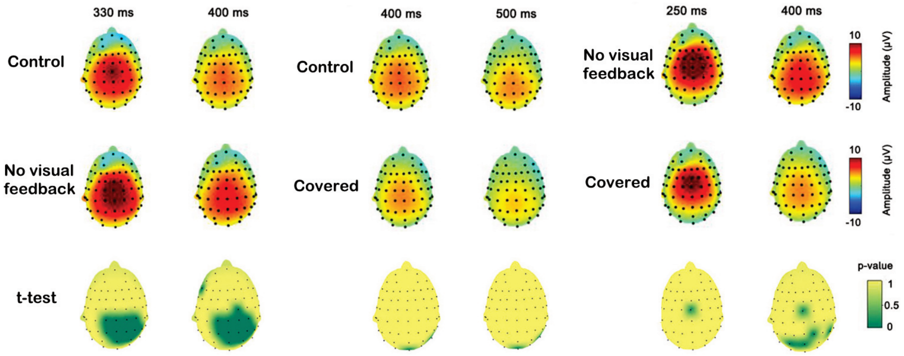
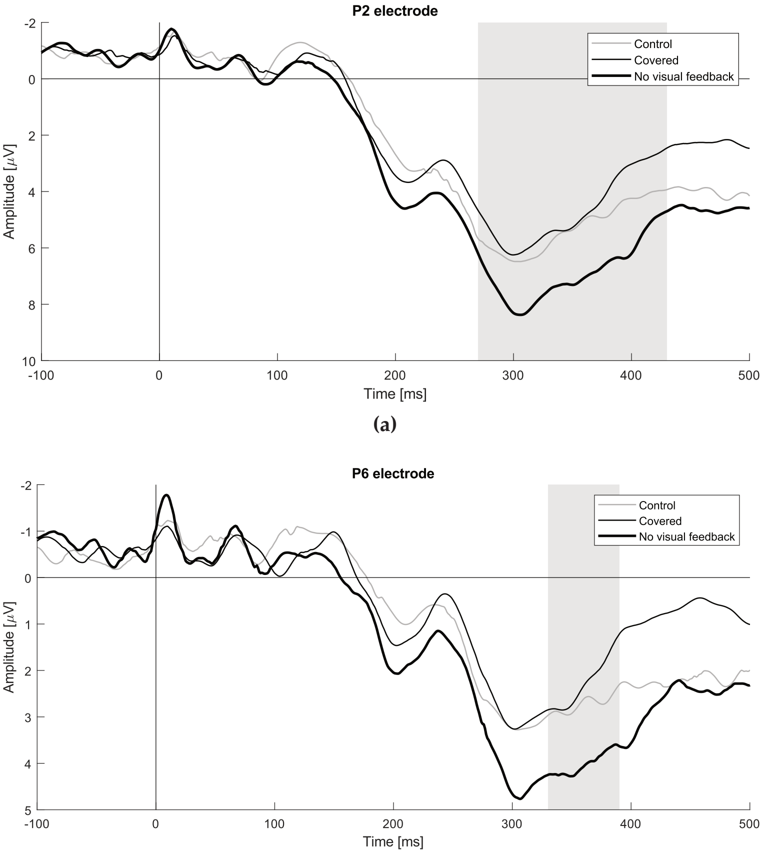


Fig. 3.12: Topographies of the grand mean average ERPs at relevant time points chosen based on when significant differences were observed. T-tests were performed between the grand mean averages and are shown in the last row (each t-test in the bottom row, is a comparison between the two topographies in the same column). Unwanted signal components, such as eye blinks, were removed based on an Independent Component Analysis (ICA) before comparison.

dedicated to localization (Andersen, 2011). These areas could be involved in the observed differences.

Finally, the pain VAS scores from the electrical stimuli did not show any differences. The concentric electrode used in this study, required a low stimulation intensity to increase the specificity of stimulating superficial skin-layer nociceptors. These low intensities resulted in quite low pain ratings and this may be a reason that no changes were observed. Furthermore, had the intensity been greater, the ERPs could have been greater in amplitude and perhaps revealed more features of the neural underpinnings.

In sum, the perceptual changes observed in the no visual feedback condition are also reflected in cortical processing of electrical stimulus applied to visually missing area. Interestingly, the perceived location of the stimuli, measured by the same proprioceptive approach as for measuring the finger locations, also drifted significantly in the no visual feedback condition compared to the control condition.



(a)

(b)

Fig. 3.13: Grand average of ERPs of the (a) P2 and (b) P6 electrode, located over the SPL and the IPL. The grey areas mark a significant difference in amplitude between the control and no visual feedback found using a cluster-based permutation test at the significance level $\alpha = 0.05$.

Chapter 4

Investigating PLP through manipulation of visual feedback

Several approaches based on visual feedback and concurrent movements of the phantom have been used in both research and management of PLP.In this chapter, these approaches are discussed together with their contributions to the field of PLP research in section 4.1. Following an introduction to these works, the final section (section 4.2) describes the culmination of the present work: the application of the AR system developed in Study I as an intervention for PLP.

4.1 Targeting cortical representations of the missing limb

Most of the research using visual feedback (and motor-facilitated variants thereof) have sought to reduce phantom limb pain by targeting the neural circuits previously associated to the missing limb (Chan et al., 2007a; Murray et al., 2007; Cole et al., 2009; Schmalzl et al., 2013; Foell et al., 2014; Ortiz-Catalan et al., 2014b; Mercier and Sirigu, 2009; Mouraux et al., 2016; Ortiz-Catalan et al., 2016). This line of study was sparked by the invention of the mirror box illusion (Ramachandran and Rogers-Ramachandran, 1996), that showed remarkable results in case-studies on individuals with PLP, and the concurrent discovery of cortical reorganization in amputees, which correlated well with the average intensity of PLP (Flor et al., 1995; Lotze et al., 1999; Foell et al., 2014).

In recent years, the maladaptive plasticity theory of Flor et al. (1995) has come under critique for being based on correlations by Makin et al. (2013). In their work, they present data suggesting that preserved function of the cortical representation of the missing limb is associated to increased levels of PLP. The study, however, received some critique (Flor et al., 2013), as the authors had used imagined movements made by healthy controls in comparison to executed phantom movements made by the amputees. It was shown, in previous study by (Raffin et al., 2012), that amputees can perform both imagined and execute phantom movements, and that these activate differently, thus questioning the validity of the comparisons made by Makin et al. (2013).

Following, Makin et al. (2015b) published a new study suggesting that a reorganization *is* happening following amputation, but that the cortical shift is not significantly correlated to PLP and of less magnitude than previously reported. Instead, Makin et al. (2015a) points to network-level reorganizations, were the representation of the amputated limb is decoupled from the sensorimotor network and instead coupled to the default mode network. The idea that network level effects are present has been proposed before (Flor et al., 2006), but the results presented by Makin et al. (2015a) demonstrated their existence. Hence, the exact underpinnings of a cortical origin of PLP is still to be determined, but as of yet, the aim of visual feedback methods is still relevant, as these methods aim to reengage the neural circuits of the amputated limb - an aim that is encouraged by most authors, irrespective of the theory for which they argue (Moseley and Flor, 2012; Raffin et al., 2016; Kikkert et al., 2017; Andoh et al., 2018; Van Den Heiligenberg et al., 2018; Ortiz-Catalan, 2018).

4.1.1 AR, VR and motor-facilitated imagery for PLP management

The use of mirror therapy for PLP management has the limitation, that the movements performed by the amputee have to be synchronous and mirrored for the mirror image of the healthy limb to "come alive", a limitation that can be problematic especially for lower-limb amputees, where mirror movements can seem unnatural. Furthermore, Raffin et al. (2012) showed that there is a distinct difference between imagined and executed movements of phantoms, and it questions whether mirror therapy results in executed or imagined movements of the phantom.

To overcome this problem, control of the phantom visualization has to be transferred to the residual limb, such that the visualization will only move, if the residual limb commands it. This necessitates the move from a mirror as the visualization medium to display technologies, which was done initially by Murray et al. (2006, 2007), who implemented a mirror box in VR. Control of the phantom visualization was still performed from the intact limb, rather than the residual limb. The transfer of control started with the study of Cole et al. (2009), where a virtual hand was displayed in an HMD and a set of preprogrammed movements were performed by the virtual hand, based on the position of the residual limb in relation to objects. The authors reported immediate pain decrease in a group of seven amputees with PLP when they were immersed in the VR visualization. They further remarked that the more amputees gained a sense of agency and virtual immersion, the greater the beneficial effects were.

Many variations on VR systems (Mercier and Sirigu, 2009; Wake et al., 2015; Osumi et al., 2017; Mouraux et al., 2016; Perry et al., 2018), flat-screen AR (Desmond et al., 2006; Penelle et al., 2012; Ortiz-Catalan et al., 2014b, 2016; De Nunzio et al., 2018) and AR HMD systems (Bach et al., 2010; Trojan et al., 2014; Carrino et al., 2014) have appeared (for a slightly out of date review, see (Dunn et al., 2017) and see subsection 3.1.1, chapter 3). These latter studies with AR have introduced EMG control over the phantom visualizations (Alphonso et al., 2012; Ortiz-Catalan et al., 2014b, 2016; De Nunzio et al., 2018), as well as the addition of tactile feedback (Wake et al., 2015; Osumi et al., 2017; De Nunzio et al., 2018). The reported effects of those of the treatments with prolonged intervention seem to average about 30% pain reductions.

4.2 Individually optimized AR in the pursuit of agency and embodiment

The mirror box illusion presents yet another problem for the subgroup of amputees with PLP who experience telescoped phantoms. The perception of a telescoped phantom may not be as easily associated to the mirror image of the intact hand, as in amputees without this perception. This was evident in the mirror box illusion study by Foell et al. (2014), where the amputees with telescoping had no pain reductions, compared to those with extended phantoms whom experienced about 50% pain reductions. Several studies point to that the ability to immerse oneself and the sense agency over the phantom are important factors to obtain pain relief from these approaches (Cole et al., 2009; Mercier and Sirigu, 2009; Trojan et al., 2014; Foell et al., 2014; Wake et al., 2015; Osumi et al., 2017).

In an editorial symposium report from EFIC 2014 on a symposium for virtual reality therapies for phantom limb pain, several of the prominent researchers in the field discussed the challenges for treating PLP using these kinds of technologies (Perry et al., 2014). In the report, it was indicated that there had been some agreement among initial experimental results, pointing to agency as an important factor in obtaining PLP alleviation. Furthermore, they highlighted the importance of monitoring other phantom phenomenon, such as telescoping during intervention.

The final study of this work, Study III, attempts to accommodate the differences in phantom perceptions while maximizing agency in an intervention for PLP.

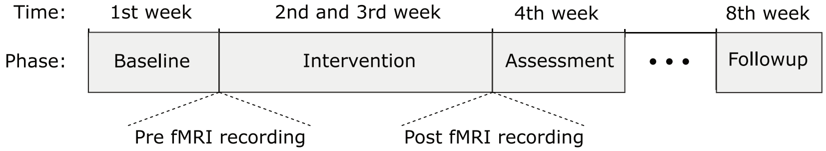


Fig. 4.1: Study III timeline.

4.2.1 Study III - Motor-facilitated, perceptually coherent visual feedback training in amputees experiencing telescoping and PLP

Study III - Experimental design. The aim of Study III was to investigate if PLP could be decreased by using a perceptually coherent, visual feedback training for amputees with PLP and telescoping. Especially, the aim was to assess the effects of the training on cortical organization, PLP decrease and their relation to agency and telescoping. To investigate these aspects, the study was designed as an intervention study with continuous monitoring of variables, and pre- and post-assessments of cortical organization. The intervention was arranged as a four-week main study period, where the: first week was a baseline week to obtain baseline measures on relevant variables; second and third week were the actual intervention period; the fourth week was used for assessment of variables post-intervention. Additionally, a short follow-up was conducted four weeks past the end of the main study. A study time line is shown in figure 4.1. Before and after the two intervention weeks, fMRI recording sessions were performed. Only upper-limb amputees experiencing both telescoping and PLP were eligible for the study.

Study III - Methods. During the entire four-week period, a pain diary was kept from which the main outcome was the following question "How strong has your phantom limb pain been today (on average)?" rated on an NRS from 0 = "Not strong at all", to 6 = "Extremely strong". The German version of the West Haven-Yale Multidimensional Pain Inventory (MPI) (Kerns et al., 1985; Flor et al., 1990), adjusted to assess PLP, was used to assess pain at baseline and assessment week and at followup. Before and after the intervention weeks fMRI recordings (Siemens 3 Tesla TRIO scanner, Siemens AG, Erlangen, Germany) were performed of the amputees performing a lip pursing task. The aim with this task was to monitor changes in the lip somatotopy, which can reflect cortical reorganization of the area previously corresponding to the amputated limb (Flor et al., 1995; Birbaumer et al., 1997; Foell et al., 2014).

The intervention consisted of eight training sessions dispersed over the two weeks that of intervention. Each training session was started and ended with questionnaires and measures to capture immediate changes due to the training. The measures before training were: the McGill Short Form questionnaire Melzack (1987); telescoping measured using both a VAS scale with the ends representing the phantom being either fully extended (identical length to the intact, contralateral limb) or entirely inside the residual limb, and finally; Telescoping measured through determining the position of landmarks of the phantom through proprioception, i.e. using a mechanism comparable to the one used in Study II (see subsection 3.2.2 in chapter 3). After the training session, the measures performed before training were repeated with the addition of the RHI questionnaire (Longo et al., 2008) adjusted slightly to accommodate amputees and phantom limbs.

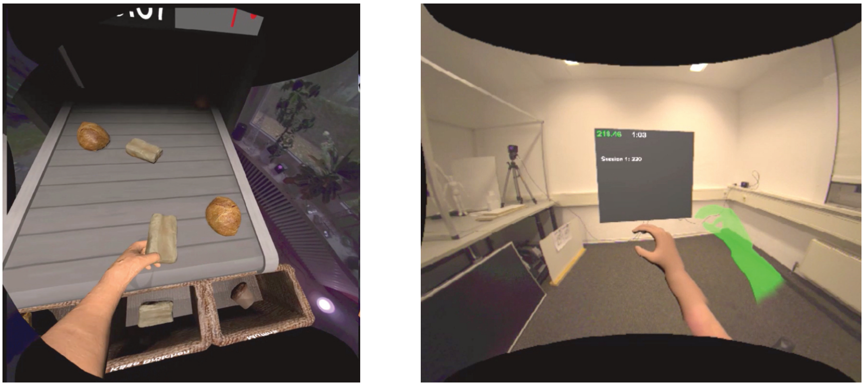
The training started by adjusting a visualization of a generic arm to fit the perceptions of the individual amputees' phantom. This was done in collaboration between the experimenter and the amputee until it coincided with the perception of the phantom. Next, the residual limb was fitted with the position and orientation tracker together with the EMG armband. To enable control of the virtual phantom from the residual limb, an algorithm had to interpret the EMG data into movements. This machine learning algorithm had to trained to work, and thus, the amputees were asked to perform a few movements to train the algorithm. The algorithm used was based on a non-negative matrix factorization by Jiang et al. (2009b, 2013).

After the algorithm was trained, the training session proceeded to the actual training, which consisted of three different tasks of five minutes each, repeated three times, i.e. $3 \times 5 \times 3 = 45\,\text{min}$. The tasks were the same as those used in Study I (see subsection 3.1.3, chapter 3): a fast paced game where the subjects had to sort bakery item into correct bins, see figure 4.2a; an imitation game, where subjects had to imitate the pose of a "ghost" hand, see figure 4.2b; and finally a pick-and-place game, where objects had to be picked up from one side of table and position precisely into a "ghost" version of the same object. All the games were scored to encourage proficient use of the virtual phantom visualization.

For statistical analysis, linear mixed models were used with the measure points as fixed factor and a random intercept for each subject, accounting for inter-individual differences.

Study III - Results. Seven amputees with PLP and telescoping completed the study.

Pain: the pain diary (averaged for each week, as is common (Foell et al., 2014)) showed a significant reduction of pain severity of 32% ($F(3, 8.004) = 14.568$, $p = 0.001$, using a diagonal covariance matrix. Significant decrease between first training week and the assessment week: $\text{MD} = -0.478$, $p = 0.018$, see figure 4.3a). A 52% pain reduction was reported with the summary score of the McGill short form pain questionnaire (also known as the pain rating index (Melzack, 1987)), measured at the beginning of each training session ($F(7, 20.527) = 4.243$, $p = 0.005$, using a first order factor analytic



(a) (b)

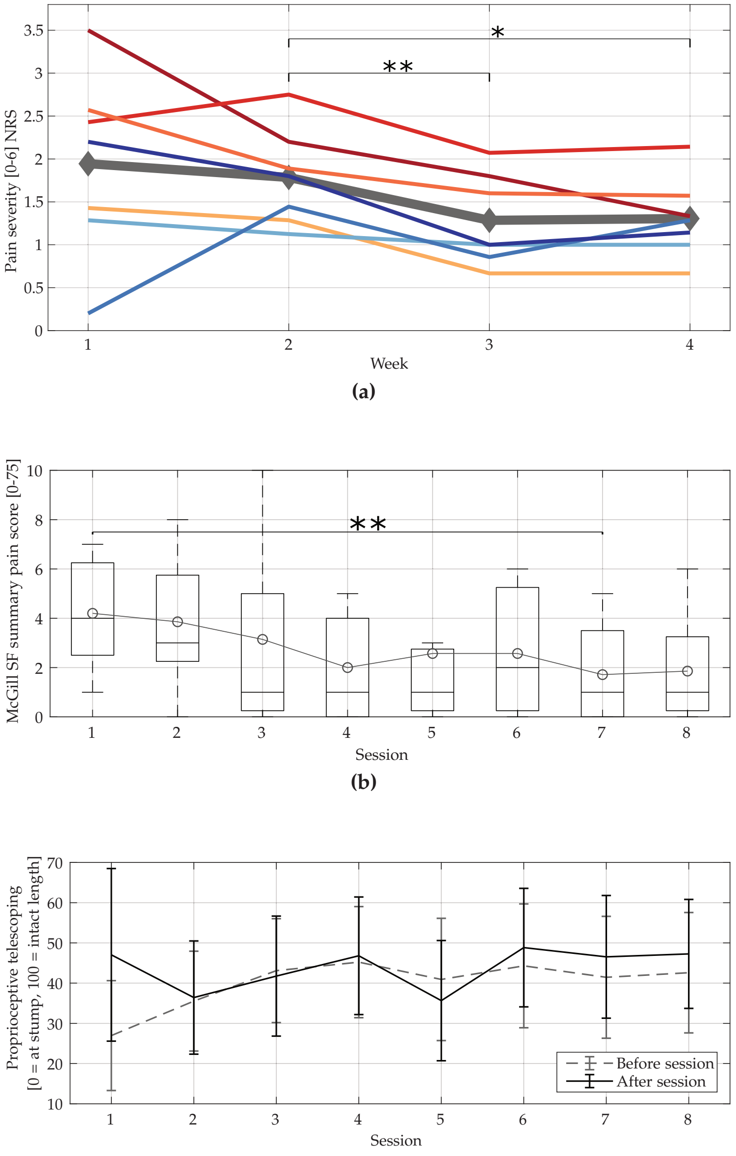
Fig. 4.2: Example view of the training that was used during Study III, both are from training sessions with the amputees. The system is stereoscopic, but for conservation of space, only the view of a single eye is displayed here. (a) shows the bakery task, in which the virtual phantom was used to sort incoming bakery items into the correct bins. (b) shows the imitation task, where precise EMG control was used to make the phantom visualization attain a similar pose as the green "ghost" phantom shown to the right.

covariance matrix. Significant decrease between initial training session and seventh training session: MD $= -1.884$, $p = 0.032$, see figure 4.3b). Despite a trend in the MPI pain severity, this measure was not significantly different ($F(2, 9.540) = 2.097$, $p = 0.270$, using a scaled identity covariance matrix).

Telescoping: Despite trends, proprioceptively measured telescoping did not change significantly (As measured before training sessions: $F(7, 22.992) = 2.116$, $p = 0.083$, and after training sessions: $F(7, 10.079) = 2.844$, $p = 0.065$, using a first order autoregressive and heterogenous first order autoregressive covariance matrix, respectively. See figure 4.3c). Felt telescoping measured using a VAS before and after training sessions did not change significantly either ($F(7, 13.926) = 0.476$, $p = 0.836$ and $F(7, 10.893) = 2.844$, $p = 0.065$ using a first order factor and a heterogenous first order autoregressive covariance matrix, respectively).

Agency, ownership, location and embodiment: Embodiment and ownership factors increased over sessions, whereas location and agency measures were dispersed over the individual sessions. The resulting F-statistics and p-values are shown in table 4.1.

Cortical changes: A significant change in cortical activity was observed at the lip-area in the somatosensory cortex of the hemisphere contralateral to amputation ([xyz: $-52, -14, 42$], $p = 0.011$), see figure 4.4a. The observed change was located superior to the intact-side lip-peak location ([xyz: $52, -10, 36$]), see figure 4.4b. Additionally, a decrease of activity correlated



(a)

(b)

(c)

Fig. 4.3: Plots of: (a) pain severity from pain diaries [0-6] NRS, coloured lines represents each individual, while the thick grey line represents the average; (b) box plots of McGill short form pain scores [0-75], with a mean line plot, measured at the beginning of training sessions, and; (c) telescoping measured using proprioception before and after session [% length of the missing limb] and whiskers corresponds to the SEM). * $= p < 0.05$ and ** $= p < 0.001$.

Factor:	Agency	Ownership	Location	Embodiment
F-statistic:	$F(7, 29.882) = 1.453$, $p = 0.222$ (AR1)	$F(7, 20) = 2.243$, $p = 0.074$ (FA1)	$F(7, 17.729) = 0.973$, $p = 0.480$ (FA1)	$F(7, 26.366) = 1.192$, $p = 0.341$ (AR1)

Table 4.1: Table of F-statistics of each factor in the RHI questionnaire (Longo et al., 2008). AR1 refers to first order autoregressive covariance matrix and FA1 refers to first order factor analytic covariance matrix.

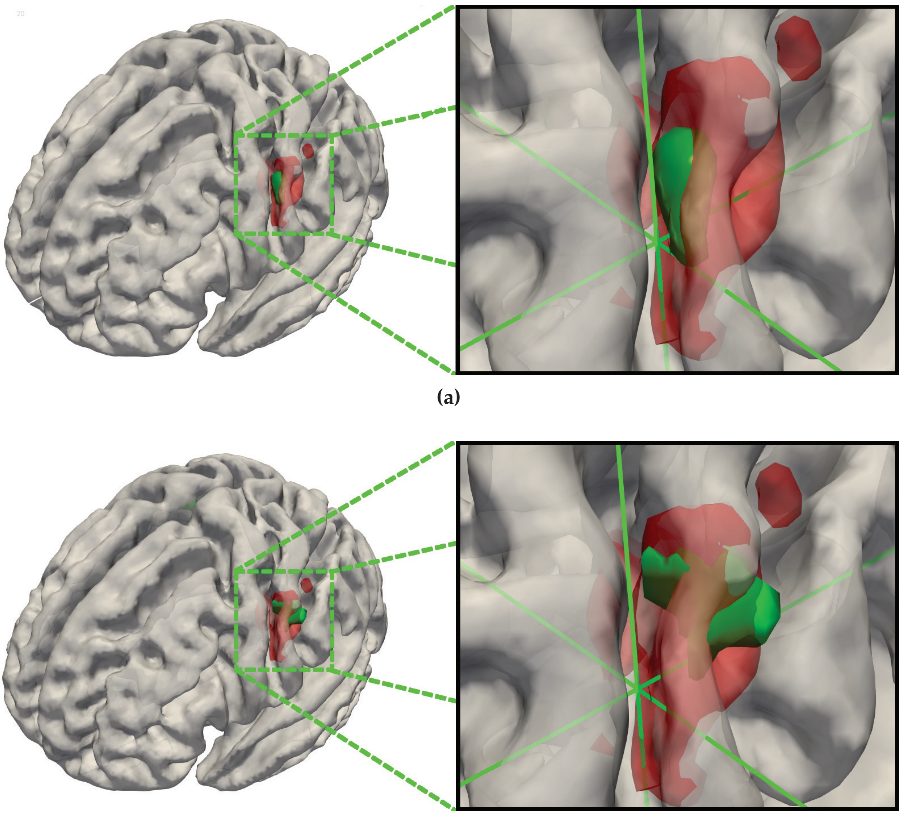
significantly with a decrease in PLP in an area, that was further superior and in the direction of the hand and wrist representation ([xyz: $-52, -16, 44$], $p = 0.023$). The peak activity of the lip pursing tasks were located and compared between the two fMRI recordings. Reliable peaks could only be located for five subjects, however, they all indicated a shift of the peak activity in SI towards the location of the contralaterally flipped, intact side, lip peak location, but it was not significant (one-tailed paired t-test: $t(4) = 2.669$, $p = 0.056$, M = 4.62, SD = 3.87).

Correlations: A main interest of this study was to assess relationships among agency, embodiment, telescoping and PLP. Note: the following correlations are based on the measures captured concomitantly at the sessions, averaged per subject over all sessions, resulting in one data-point per subject. Starting with PLP measured using McGill short form pain questionnaire summary scores, it correlated significantly with both measures of telescoping ($r = -0.695$, $p = 0.006$, and $r = -0.535$, $p = 0.049$ for felt and proprioceptive, respectively). PLP also correlated to embodiment, but not significantly to agency ($r = -0.777$, $p = 0.040$, and $r = -0.745$, $p = 0.055$, respectively). Both felt and proprioceptive telescoping correlated significantly with both embodiment and agency (proprioceptive: $r = 0.889$, $p = 0.007$, and $r = 0.916$, $p = 0.004$, respectively).

The pain decrease observed after intervention demonstrated that motor-facilitated visual feedback interventions can be helpful for amputees with PLP *and* telescoping, given that the visualizations are customized to the perceptions of the phantom. Telescoping showed a tendency to decrease, such that phantoms approached the length of the original limb. Telescoping has been linked to the amount of PLP before and this could be the relationship observed over the course of this intervention (Grüsser et al., 2001; Flor et al., 2006). Katz (1992) suggested that telescoping was a reflection of beneficial plasticity and that less telescoping was associated to *more* pain, however, Grüsser et al. (2001) later found a positive correlation between PLP and telescoping, but not to reorganization in SI. Instead Grüsser et al. (2001) suggested that the cortical changes responsible for telescoping might be located in the PPC. The results of this study would favor the observations of Grüsser et al. (2001).

Correlations confirm the expectation that agency and embodiment were correlated to PLP. However, this is a correlation, and it is not possible to determine if these factors are causal to PLP alleviation or if the PLP prevents embodiment and agency over the visualization. It might well be that there is a common causal mechanism for both, e.g. cortical reorganization in the neural circuitry that inhibit agency and embodiment while driving PLP.

The cortical changes observed in this study strongly suggest that a cortical reorganization occurred following the intervention. Significant changes were detected in activity decrease in an area superior to the intact side peak lip-activation, and a significant correlation between PLP and activity decrease in another area further superior to the intact side peak lip-activation. Individual peak activity localization in SI suggest a similar conclusion, with a near-significant shift in peak-activity locations from before to after intervention towards the intact side, contralaterally flipped, peak lip-activation.



(a)

(b)

Fig. 4.4: 3D images of a deprived MNI brain template (Fonov et al., 2011) with overlaid 3D structures of the areas of significant change during lip pursing from before to after intervention in the Primary Somatosensory Cortex. The zoomed-in images depict the post-central gyrus in the center. The green crosshair shows the peak activity in the hemisphere ipsilateral to amputation, flipped to the contralateral hemisphere, i.e. this corresponds to the "healthy" peak activation for the lip ([xyz: $52, -10, 36$]). The red shaded area corresponds to the area activated significantly post intervention ($Z > 2.3$). The green structures, superior to the green crosshair, marks in (a) the area were a significant decrease in activity was observed after the intervention ([xyz: $-52, -14, 42$], $p = 0.011$) and in (b) a significant covariance to the pain severity decrease from the pain diary [xyz: $-52, -16, 44$], $p = 0.023$), i.e. a decrease in activation in this area corresponded significantly to a decrease in pain severity scores from the pain diaries.

Chapter 5

Synthesis

Through this work, the influence of visual feedback in phantom limb pain and perception has been investigated. By using a custom-built, novel AR and MR system, it was possible to manipulate visual feedback, both by adding a visualization of a phantom limb and by realistic removal of visual feedback from a limb. These manipulations were used to investigate whether it was possible to change the body perception and pain in both amputees and healthy participants. Our findings on healthy participants (Study IIA and IIB), showed significant mislocalization of the distal parts of the limb, indicating that such changes occurred. Additionally, scores from questionnaires showed a disownership of the limb and some perceptual experiences that resemble the telescoping phenomenon often observed in amputees with phantom limbs. By using the same visual manipulation, the cortical response to nociception-specific electrical stimuli was investigated in the absence of visual feedback from the stimulated limb. While the absence of visual feedback was not reflected by changes in VAS pain scores, there were clear effects in cortical response over the parietal area. These changes were also reflected when subjects attempted to determined the position of the stimuli through proprioception, with a significant shift in localization towards the visual "amputation" site. These results showed that it is possible to change body perceptions in healthy subjects, but the experimental pain was not significantly affected by such visual manipulation. One possible reason could be due to the methodological paradigm; the low stimulation intensities were not able to target nociceptive fibers specifically.

In amputees with PLP and telescoping, the results of Study III indicated a clear pain relief of up to 52% by using perceptually coherent, motor-facilitated visual feedback training. Additionally, significant changes in cortical activity were observed in SI, which likely reflect a cortical reorganization due to the intervention. Hence, Study III showed that it is possible to influence the organization of cortical areas through the use of cross-modal visual feedback training. Furthermore, the results pointed to a relationship between both PLP, telescoping and embodiment.

The outcome of this work argues for an important contribution of visual feedback. It is apparent, in healthy individuals, that own-limb visual feedback activates cortical areas differently as compared with not having visual feedback (Study IIB) or viewing a limb from an allocentric viewpoint (Kennett et al., 2001; Taylor-Clarke et al., 2002; Saxe et al., 2006). Additionally, manipulating the visual aesthetic of the arm has been shown to move the epicenter of activity in SI (Schaefer et al., 2007, 2009, 2013). In a recently proposed hypothesis, Ortiz-Catalan (2018), argued that visual feedback has no effects on PLP alleviation, however, the results presented here would argue for a different perspective. In his hypothesis, Ortiz-Catalan (2018) suggested that the neural circuitry responsible for the amputated limb enters a "state of perturbation" following amputation. In this state the neural circuitry wires, through stochastic (i.e. random) processes, to nearby areas and possibly to areas involved in pain processing. To reverse these changes, Ortiz-Catalan (2018) proposed that the opposite of the Hebbian learning principle applies, i.e. instead of "neurons that fire together, wire together": "neurons that fire apart, wire apart" (Ortiz-Catalan, 2018). And thus, by activating the dormant neural circuitry of the missing limb, the areas will "wire apart" and thereby reverse the connections created during the state of perturbation.

While the hypothesis borrowed the main concept from the maladaptive plasticity theory of Flor et al. (1995), it added specific ideas on the reversal of cortical changes that have been observed in several studies (Flor et al., 2001b; MacIver et al., 2008; Foell et al., 2014) and it would account for the heterogeneity of perceptual and painful experiences of amputees. However, if the target is to activate the dormant neural circuitry of the limb, the conclusion of Ortiz-Catalan (2018), that visual feedback is unnecessary seems contradictory. Through this and other work, there is evidence that argue for an excitatory effect of seeing an egocentrically arranged limb (Saxe et al., 2006) and modulatory response to stimuli (Kennett et al., 2001; Taylor-Clarke et al., 2002)(Study IIB). Furthermore, two randomized controlled trials have found that visual feedback was necessary in generating the beneficial effects of mirror therapy (Chan et al., 2007a; Finn et al., 2017). Thus, visual feedback seems to be an important factor in interventions for PLP.

The study of Ortiz-Catalan et al. (2016) and Study III employed systems relying on similar mechanisms and showed comparable results: 52% decrease in pain rating index for two-weeks of intervention and 51% decrease in pain rating index for six-weeks of intervention, respectively. These are encouraging results, however, these interventions must be tested in a randomized controlled trials against e.g., regular mirror therapy, to verify that these methods increase efficiency. Further studies should strive to discern the effects of the mechanisms used in this type of study, i.e., motor-execution, visual feedback, agency and ownership. Not only will this isolate efficient treatment targets, but equally important, it will help to elucidate the underlying nature of PLP.

References

Alphonso, A. L., Monson, B. T., Zeher, M. J., Armiger, R. S., Weeks, S. R., Burck, J. M., Moran, C., Davoodie, R., Loeb, G., Pasquina, P. F., and Tsao, J. W. (2012). Use of a virtual integrated environment in prosthetic limb development and phantom limb pain. *Studies in Health Technology and Informatics*, 181:305–309.

Andersen, R. A. (2011). Inferior Parietal Lobule Function in Spatial Perception and Visuomotor Integration. *Comprehensive Physiology*.

Andoh, J., Milde, C., Tsao, J. W., and Flor, H. (2018). Cortical plasticity as a basis of phantom limb pain: Fact or fiction? *Neuroscience*, 387:85–91.

Anthes, C., García-Hernández, R. J., Wiedemann, M., and Kranzlmüller, D. (2016). State of the art of virtual reality technology. *IEEE Aerospace Conference Proceedings*, 2016-June.

Assal, F., Schwartz, S., and Vuilleumier, P. (2007). Moving with or without will: Functional neural correlates of alien hand syndrome. *Annals of Neurology*, 62(3):301–306.

Aukstakalnis, S. (2016). *Practical Augmented Reality: A Guide to the Technologies, Applications, and Human Factors for AR and VR*.

Bach, F., Schmitz, B., Maaß, H., Çakmak, H., Diers, M., B.-Bodmann, R., Kamping, S., and Flor, H. (2010). Using Interactive Immersive VR/AR for the Therapy of Phantom Limb Pain. In *Proceedings of the 13th International Conference on Humans and Computers*, pages 183–187, Aizu-Wakamatsu, Japan. University of Aizu Press.

Bæk Hansen, T., Christian Kjeldsen, H., and Wong, C. (2018). Amputationer. https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/fysmed-og-rehab/tilstande-og-sygdomme/rehabilitering/amputationer/ Last accessed on Dec 20, 2018.

Balk, S. a., Bertola, M. A., and Inman, V. W. (2013). Simulator sickness questionnaire: Twenty years later. *Proceedings of the Seventh International Driving Symposium on Human Factors in Driver Assessment, Training, and Vehicle Design*, pages 257–263.

Bear, M. F., Connors, B. W., and Paradiso, M. A. (2001). *Neuroscience: Exploring the brain*. Lippincott Williams & Wilkins, 2 edition.

Bekrater-Bodmann, R., Foell, J., Diers, M., Kamping, S., Rance, M., Kirsch, P., Trojan, J., Fuchs, X., Bach, F., Çakmak, H. K., Maaß, H., and Flor, H. (2014). The Importance of Synchrony and Temporal Order of Visual and Tactile Input for Illusory Limb Ownership Experiences – An fMRI Study Applying Virtual Reality. *PLoS ONE*, 9(1):e87013.

Berlucchi, G. and Aglioti, S. M. (2010). The body in the brain revisited. *Experimental Brain Research*, 200(1):25–35.

Birbaumer, N., Lutzenberger, W., Montoya, P., Larbig, W., Unertl, K., Töpfner, S., Grodd, W., Taub, E., and Flor, H. (1997). Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 17(14):5503–8.

Blanke, O., Ortigue, S., Landis, T., and Seeck, M. (2002). Stimulating illusory own-body perceptions. *Nature*, 419(6904):269–270.

Bohil, C. J., Alicea, B., and Biocca, F. A. (2011). Virtual reality in neuroscience research and therapy. *Nature Reviews Neuroscience*, 12(12).

Botvinick, M. and Cohen, J. (1998). Rubber hands 'feel' touch that eyes see. *Nature*, 391(6669):756.

Carrino, F., Rizzotti, D., Gheorghe, C., and Bakajika, P. K. (2014). Augmented Reality Treatment for Phantom Limb Pain. *Applications of Virtual and Augmented Reality*, pages 248–257.

Chan, B. L., Witt, R., Charrow, A. P., Magee, A., Howard, R., Pasquina, P. F., Heilman, K. M., and Tsao, J. W. (2007a). Mirror therapy for phantom limb pain. *New England Journal of Medicine*, 357(21):2206–2207.

Chan, E. A., Chung, J. W., Wong, T. K., Lien, A. S., and Yang, J. Y. (2007b). Application of a virtual reality prototype for pain relief of pediatric burn in Taiwan. *Journal of Clinical Nursing*, 16(4):786–793.

Chessa, M., Maiello, G., Borsari, A., and Bex, P. J. (2016). The Perceptual Quality of the Oculus Rift for Immersive Virtual Reality. *Human-Computer Interaction*, 00(00):1–32.

Cole, J., Crowle, S., Austwick, G., Henderson Slater, D., and Slater, D. H. (2009). Exploratory findings with virtual reality for phantom limb pain; from stump motion to agency and analgesia. *Disability and rehabilitation*, 31(10):846–854.

Cole, J. and Paillard, J. (1995). *The Body and the Self*. MIT Press.

David, N., Cohen, M. X., Newen, A., Bewernick, B. H., Shah, N. J., Fink, G. R., and Vogeley, K. (2007). The extrastriate cortex distinguishes between the consequences of one's own and others' behavior. *NeuroImage*, 36(3):1004–1014.

David, N., Newen, A., and Vogeley, K. (2008). The "sense of agency" and its underlying cognitive and neural mechanisms. *Consciousness and Cognition*, 17(2):523–534.

De Nunzio, A. M., Schweisfurth, M. A., Ge, N., Falla, D., Hahne, J. M., Godecke, K., Petzke, F., Siebertz, M., Dechent, P., Weiss, T., Flor, H., Graimann, B., Aszmann, O., and Farina, D. (2018). Relieving Phantom Limb Pain with Multimodal Sensory-Motor Training. *Journal of neural engineering*.

de Vignemont, F. (2011). Embodiment, ownership and disownership. *Consciousness and Cognition*, 20(1):82–93.

Desmond, D. M., O'Neill, K., De Paor, A., McDarby, G., MacLachlan, M., Og'Neill, K., De Paor, A., McDarby, G., and MacLachlan, M. (2006). Augmenting the Reality of Phantom Limbs: Three Case Studies Using an Augmented Mirror Box Procedure. *JPO Journal of Prosthetics and Orthotics*, 18(3):74–79.

Diers, M., Zieglgänsberger, W., Trojan, J., Drevensek, A. M., Erhardt-Raum, G., and Flor, H. (2013). Site-specific visual feedback reduces pain perception. *Pain*, 154(6):890–896.

Duhamel, J.-R., Colby, C. L., and Goldberg, M. E. (1998). Ventral Intraparietal Area of the Macaque: Congruent Visual and Somatic Response Properties. *Journal of Neurophysiology*, 79(1):126–136.

Dunn, J., Yeo, E., Moghaddampour, P., Chau, B., and Humbert, S. (2017). Virtual and augmented reality in the treatment of phantom limb pain: A literature review. *NeuroRehabilitation*, 40(4):595–601.

Ehrsson, H. H. (2005). Touching a Rubber Hand: Feeling of Body Ownership Is Associated with Activity in Multisensory Brain Areas. *Journal of Neuroscience*, 25(45):10564–10573.

Ehrsson, H. H., Spence, C., and Passingham, R. E. (2004). That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. *Science (New York, NY)*, 305(5685):875–877.

Elbert, T., Flor, H., Birbaumer, N., Knecht, S., Hampson, S., Larbig, W., and Taub, E. (1994). Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. *NeuroReport*, 5(18):2593–2597.

Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., and Taub, E. (1995). Increased Cortical Representation of the Fingers of the Left Hand in String Players. *Science*, 270(5234):305–307.

Ernst, M. O. and Banks, M. S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature*, 415(6870):429–433.

Farrer, C., Franck, N., Georgieff, N., Frith, C. D., Decety, J., and Jeannerod, M. (2003). Modulating the experience of agency: A positron emission tomography study. *NeuroImage*, 18(2):324–333.

Farrer, C. and Frith, C. D. (2002). Experiencing oneself vs another person as being the cause of an action: The neural correlates of the experience of agency. *NeuroImage*, 15(3):596–603.

Finn, S. B., Perry, B. N., Clasing, J. E., Walters, L. S., Jarzombek, S. L., Curran, S., Rouhanian, M., Keszler, M. S., Hussey-Andersen, L. K., Weeks, S. R., Pasquina, P. F., and Tsao, J. W. (2017). A randomized, controlled trial of mirror therapy for upper extremity phantom limb pain in male amputees. *Frontiers in Neurology*, 8(JUL):1–7.

Flor, H. (2002). Phantom-limb pain: Characteristics, causes, and treatment. *Lancet Neurology*, 1(3):182–189.

Flor, H., Denke, C., Schaefer, M., and Grüsser, S. (2001a). Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. *The Lancet*, 357(9270):1763–1764.

Flor, H., Denke, C., Schaefer, M., and Grüsser, S. (2001b). Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. 357:1763–1764.

Flor, H., Diers, M., and Andoh, J. (2013). The neural basis of phantom limb pain. *Trends in Cognitive Sciences*, 17(7):307–308.

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumers, N., Larbig, W., and Taub, E. (1995). Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature*, 375(6531):482–484.

Flor, H., Nikolajsen, L., Jensen, T. S., Nikolajsen, L., and Staehelin Jensen, T. (2006). Phantom limb pain: a case of maladaptive CNS plasticity? *Nature Rev Sci*, 7(11):873–881.

Flor, H., Rudy, T. E., Birbaumer, N., Streit, B., and Schugens, M. M. (1990). Zur Anwendbarkeit des West Haven-Yale Multidimensional Pain Inventory im deutschen Sprachraum - Daten zur Reliabilität und Validität des MPI-D. *Der Schmerz*, 4(2):82–87.

Foell, J., Bekrater-Bodmann, R., Diers, M., and Flor, H. (2014). Mirror therapy for phantom limb pain: Brain changes and the role of body representation. *European Journal of Pain*, 18(5):729–739.

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., and Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage*, 54(1):313–327.

Fuchs, X., Riemer, M., Diers, M., Flor, H., and Trojan, J. (2016). Perceptual drifts of real and artificial limbs in the rubber hand illusion. *Scientific Reports*, 6(August 2015):24362.

Gallagher, S. (2005). *How the Body Shapes the Mind*. Oxford University Press.

Gallagher, S. and Gallagher (2000). Philosophical conceptions of the self: Implications for cognitive science. *Trends in Cognitive Sciences*, 4(1):14–21.

Giummarra, M. J., Gibson, S. J., Georgiou-Karistianis, N., and Bradshaw, J. L. (2007). Central mechanisms in phantom limb perception: The past, present and future. *Brain Research Reviews*, 54(1):219–232.

Giummarra, M. J., Gibson, S. J., Georgiou-Karistianis, N., and Bradshaw, J. L. (2008). Mechanisms underlying embodiment, disembodiment and loss of embodiment. *Neuroscience and Biobehavioral Reviews*, 32(1):143–160.

Grüsser, S. M., Winter, C., Mühlnickel, W., Denke, C., Karl, A., Villringer, K., and Flor, H. (2001). The relationship of perceptual phenomena and cortical reorganization in upper extremity amputees. *Neuroscience*, 102(2):263–272.

Guéniot, T. (1861). D'une hallucination du toucher (hétérotopie subjective des extrémités) particulière à certains amputés. *Journal de l'anatomie et de la physiologie normales et pathologiques de l'homme et des animaux*, 4:416–418.

Hanley, M. A., Ehde, D. M., Jensen, M., Czerniecki, J., Smith, D. G., and Robinson, L. R. (2009). Chronic Pain Associated with Upper-Limb Loss. *American Journal of Physical Medicine & Rehabilitation*, 88(9):742–751.

Hänsel, A., Lenggenhager, B., Von Känel, R., Curatolo, M., and Blanke, O. (2011). Seeing and identifying with a virtual body decreases pain perception. *European Journal of Pain*, 15(8):874–879.

Harris, A. J. (1999). Cortical origin of pathological pain. *Lancet*, 354(9188):1464–1466.

Henderson, W. and Smyth, G. E. (1948). PHANTOM LIMBS. *Journal of Neurology, Neurosurgery, and Psychiatry*, 11(2):88–112.

Hodzic, A., Kaas, A., Muckli, L., Stirn, A., and Singer, W. (2009). Distinct cortical networks for the detection and identification of human body. *NeuroImage*, 45(4):1264–1271.

Inui, K., Tran, T. D., Hoshiyama, M., and Kakigi, R. (2002). Preferential stimulation of Aδ fibers by intra-epidermal needle electrode in humans. *Pain*, 96(3):247–252.

Islam, S., Ionescu, B., Gadea, C., and Ionescu, D. (2016). Indoor positional tracking using dual-axis rotating laser sweeps. In *2016 IEEE International Instrumentation and Measurement Technology Conference Proceedings*, volume 2016-July, pages 1–6. IEEE.

Jensen, T. S., Krebs, B., Nielsen, J., and Rasmussen, P. (1983). Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation. *Pain*, 17(3):243–256.

Jiang, N., Englehart, K. B., and Parker, P. A. (2009a). Extracting simultaneous and proportional neural control information for multiple-dof prostheses from the surface electromyographic signal. *IEEE Transactions on Biomedical Engineering*, 56(4):1070–1080.

Jiang, N., Parker, P. A., and Englehart, K. B. (2009b). Spectrum of the nonstationary electromyographic signal modelled with integral pulse frequency modulation and its application to estimating neural drive information. *Journal of Electromyography and Kinesiology*, 19(4):e267–e279.

Jiang, N., Rehbaum, H., Vujaklija, I., Graimann, B., and Farina, D. (2013). Intuitive, Online, Simultaneous and Proportional Myoelectric Control Over Two Degrees of Freedom in Upper Limb Amputees. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 22(3):501–510.

Kalckert, A. and Ehrsson, H. H. (2012). Moving a Rubber Hand that Feels Like Your Own: A Dissociation of Ownership and Agency. *Frontiers in Human Neuroscience*, 6(March):1–14.

Kalckert, A. and Ehrsson, H. H. (2014). The spatial distance rule in the moving and classical rubber hand illusions. *Consciousness and Cognition*, 30:118–132.

Kammers, M. P. M., Rose, K., and Haggard, P. (2011). Feeling numb: Temperature, but not thermal pain, modulates feeling of body ownership. *Neuropsychologia*, 49(5):1316–1321.

Katz, D. (1921). *Zur Psychologie des Amputierten und seiner Prothese*, volume 25.

Katz, J. (1992). Psychophysiological contributions to phantom limbs. *Canadian Journal of Psychiatry*, 37(5):282–298.

Katz, J. and Melzack, R. (1990). Pain 'memories' in phantom limbs: Review and clinical observations. *Pain*, 43(3):319–336.

Katz, J. and Melzack, R. (1991). Auricular transcutaneous electrical nerve stimulation (TENS) reduces phantom limb pain. *Journal of Pain and Symptom Management*, 6(2):73–83.

Kennedy, R. S., Lane, N. E., Berbaum, K. S., and Lilienthal, M. G. (1993). Simulator Sickness Questionnaire: An Enhanced Method for Quantifying Simulator Sickness. *The International Journal of Aviation Psychology*, 3(3):203–220.

Kennett, S., Taylor-Clarke, M., and Haggard, P. (2001). Noninformative vision improves the spatial resolution of touch in humans. *Current Biology*, 11(15):1188–1191.

Kerns, R. D., Turk, D. C., and Rudy, T. E. (1985). The West Haven-Yale Multidimensional Inventory (WHYMPI). *Pain*, 23:345–356.

Kikkert, S., Mezue, M., Henderson Slater, D., Johansen-Berg, H., Tracey, I., and Makin, T. R. (2017). Motor correlates of phantom limb pain. *Cortex*, 95:29–36.

Kilteni, K., Maselli, A., Kording, K. P., and Slater, M. (2015). Over my fake body: body ownership illusions for studying the multisensory basis of own-body perception. *Frontiers in Human Neuroscience*, 9(March).

Klein, T. (2004). Perceptual Correlates of Nociceptive Long-Term Potentiation and Long-Term Depression in Humans. *Journal of Neuroscience*, 24(4):964–971.

Kooijman, C. M., Dijkstra, P. U., Geertzen, J. H., Elzinga, A., and Van Der Schans, C. P. (2000). Phantom pain and phantom sensations in upper limb amputees: An epidemiological study. *Pain*, 87(1):33–41.

Kreylos, O. (2015). On the road for VR: Microsoft HoloLens at Build 2015, San Francisco. http://doc-ok.org/?p=1223 Last accessed on Dec 20, 2018.

Lelic, D., Mørch, C. D., Hennings, K., Andersen, O. K., and M. Drewes, A. (2012). Differences in perception and brain activation following stimulation by large versus small area cutaneous surface electrodes. *European Journal of Pain (United Kingdom)*, 16(6):827–837.

Lenggenhager, B., Tadi, T., Metzinger, T., and Blanke, O. (2007). Video Ergo Sum: Manipulating Bodily Self-Consciousness. *Science*, 317(5841):1096–1099.

Limanowski, J. and Blankenburg, F. (2016). Integration of Visual and Proprioceptive Limb Position Information in Human Posterior Parietal, Premotor, and Extrastriate Cortex. *Journal of Neuroscience*, 36(9):2582–2589.

Longo, M. R., Betti, V., Aglioti, S. M., and Haggard, P. (2009). Visually Induced Analgesia: Seeing the Body Reduces Pain. *Journal of Neuroscience*, 29(39):12125–12130.

Longo, M. R., Iannetti, G. D., Mancini, F., Driver, J., and Haggard, P. (2012). Linking Pain and the Body: Neural Correlates of Visually Induced Analgesia. *Journal of Neuroscience*, 32(8):2601–2607.

Longo, M. R., Schüür, F., Kammers, M. P., Tsakiris, M., and Haggard, P. (2008). What is embodiment? A psychometric approach. *Cognition*, 107(3):978–998.

Lotze, M., Flor, H., Grodd, W., Larbig, W., and Birbaumer, N. (2001). Phantom movements and pain. An fMRI study in upper limb amputees. *Brain : a journal of neurology*, 124(Pt 11):2268–2277.

Lotze, M., Grodd, W., Birbaumer, N., Erb, M., Huse, E., and Flor, H. (1999). Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? *Nature neuroscience*, 2(6):501–502.

MacIver, K., Lloyd, D. M., Kelly, S., Roberts, N., and Nurmikko, T. (2008). Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. *Brain*, 131(8):2181–2191.

Makin, T. R., Filippini, N., Duff, E. P., Henderson Slater, D., Tracey, I., and Johansen-Berg, H. (2015a). Network-level reorganisation of functional connectivity following arm amputation. *NeuroImage*, 114:217–225.

Makin, T. R., Scholz, J., Filippini, N., Henderson Slater, D., Tracey, I., and Johansen-Berg, H. (2013). Phantom pain is associated with preserved structure and function in the former hand area. *Nature Communications*, 4(1):1570.

Makin, T. R., Scholz, J., Henderson Slater, D., Johansen-Berg, H., and Tracey, I. (2015b). Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation. *Brain*, 138(8):2140–2146.

Mancini, F., Longo, M. R., Kammers, M. P. M., and Haggard, P. (2011). Visual distortion of body size modulates pain perception. *Psychological science*, 22(3):325–330.

Martini, M. (2016). Real, rubber or virtual: The vision of "one's own" body as a means for pain modulation. A narrative review. *Consciousness and Cognition*, 43:143–151.

Martini, M., Perez-Marcos, D., and Sanchez-Vives, M. V. (2014). Modulation of pain threshold by virtual body ownership. *European Journal of Pain*, 18(7):1040–1048.

Melzack, R. (1987). The short-form McGill pain questionnaire. *Pain*, 30(2):191–197.

Melzack, R. (1990). Phantom limbs and the concept of a neuromatrix. *Trends in neurosciences*, 13(3):88–92.

Melzack, R. (2001). Pain and the neuromatrix in the brain. *Journal of dental education*, 65(12):1378–1382.

Mercier, C. and Sirigu, A. (2009). Training With Virtual Visual Feedback to Alleviate Phantom Limb Pain. *Neurorehabilitation and Neural Repair*, 23(6):587–594.

Milgram, P., Takemura, H., Utsumi, A., and Kishino, F. (1994). Augmented Reality: A Class of Displays on the Reality-Virtuality Continuum. *Systems Research*, 2351(Telemanipulator and Telepresence Technologies):282–292.

Miller, J., Baiotto, H., MacAllister, A., Hoover, M., Evans, G., Schlueter, J., Kalivarapu, V., and Winer, E. (2017). Comparison of a virtual game-day experience on varying devices. *IS and T International Symposium on Electronic Imaging Science and Technology*, Part F1300:30–37.

Mitchell, S. (1872). *Injuries of Nerves and Their Consequences*. J. B. Lippincott & Co., Philadelphia.

Moseley, G. L. (2004). Graded motor imagery is effective for long-standing complex regional pain syndrome: A randomised controlled trial. *Pain*, 108(1-2):192–198.

Moseley, G. L. and Flor, H. (2012). Targeting Cortical Representations in the Treatment of Chronic Pain: A Review. *Neurorehabilitation and Neural Repair*, 26(6):646–652.

Moseley, G. L., Gallace, A., and Iannetti, G. D. (2012a). Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. *Brain*, 135(12):3676–3686.

Moseley, G. L., Gallace, A., and Spence, C. (2012b). Bodily illusions in health and disease: Physiological and clinical perspectives and the concept of a cortical 'body matrix'. *Neuroscience and Biobehavioral Reviews*, 36(1):34–46.

Moseley, G. L., Olthof, N., Venema, A., Don, S., Wijers, M., Gallace, A., and Spence, C. (2008a). Psychologically induced cooling of a specific body part caused by the illusory ownership of an artificial counterpart. *Proceedings of the National Academy of Sciences of the United States of America*, 105(35):13169–73.

Moseley, G. L., Zalucki, N. M., and Wiech, K. (2008b). Tactile discrimination, but not tactile stimulation alone, reduces chronic limb pain. *Pain*, 137(3):600–608.

Mouraux, D., Brassinne, E., Sobczak, S., Nonclercq, A., Warzée, N., Sizer, P. S., Tuna, T., and Penelle, B. (2016). 3D augmented reality mirror visual feedback therapy applied to the treatment of persistent, unilateral upper extremity neuropathic pain: a preliminary study. *Journal of Manual & Manipulative Therapy*, 9817(May):1–7.

Murray, C., Patchick, E., and Pettifer, S. (2006). Investigating the efficacy of a virtual mirror box in treating phantom limb pain in a sample of chronic sufferers. *Int J Disabil Human Dev*, 5(3):227–234.

Murray, C. D., Pettifer, S., Howard, T., Patchick, E. L., Caillette, F., Kulkarni, J., and Bamford, C. (2007). The treatment of phantom limb pain using immersive virtual reality: three case studies. *Disability and rehabilitation*, 29(18):1465–1469.

Ortiz-Catalan, M. (2018). The Stochastic Entanglement and Phantom Motor Execution Hypotheses: A Theoretical Framework for the Origin and Treatment of Phantom Limb Pain. *Frontiers in Neurology*, 9(SEP):1–16.

Ortiz-Catalan, M., Guðmundsdóttir, R. A., Kristoffersen, M. B., Zepeda-Echavarria, A., Caine-Winterberger, K., Kulbacka-Ortiz, K., Widehammar, C., Eriksson, K., Stockselius, A., Ragnö, C., Pihlar, Z., Burger, H., and Hermansson, L. (2016). Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: a single group, clinical trial in patients with chronic intractable phantom limb pain. *The Lancet*, 388(10062):2885–2894.

Ortiz-Catalan, M., Hkansson, B., and Brnemark, R. (2014a). Real-Time and Simultaneous Control of Artificial Limbs Based on Pattern Recognition Algorithms. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 22(4):756–764.

Ortiz-Catalan, M., Sander, N., Kristoffersen, M. B., Håkansson, B., and Brånemark, R. (2014b). Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: a case study of a chronic PLP patient. *Frontiers in Neuroscience*, 8(8 FEB):1–7.

Osumi, M., Ichinose, A., Sumitani, M., Wake, N., Sano, Y., Yozu, A., Kumagaya, S., Kuniyoshi, Y., and Morioka, S. (2017). Restoring movement representation and alleviating phantom limb pain through short-term neurorehabilitation with a virtual reality system. *European Journal of Pain (United Kingdom)*, 21(1):140–147.

Osumi, M., Imai, R., Ueta, K., Nobusako, S., and Morioka, S. (2014). Negative body image associated with changes in the visual body appearance increases pain perception. *PLoS ONE*, 9(9):e107376.

Penelle, B., Mouraux, D., Brassinne, E., Tuna, T., Nonclercq, A., and Warzée, N. (2012). 3D augmented reality applied to the treatment of neuropathic pain. *Virtual Reality & Associated Technologies Laval 2012 ICDVRAT2012 ICDVRAT*, pages 10–12.

Perry, B. N., Armiger, R. S., Wolde, M., McFarland, K. A., Alphonso, A. L., Monson, B. T., Pasquina, P. F., and Tsao, J. W. (2018). Clinical trial of the virtual integration environment to treat phantom limb pain with upper extremity amputation. *Frontiers in Neurology*, 9(SEP):1–9.

Perry, B. N., Mercier, C., Pettifer, S. R., Cole, J., and Tsao, J. W. (2014). Virtual reality therapies for phantom limb pain. *European Journal of Pain*, 18(7):897–899 3p.

Pons, T. P., Garraghty, P. E., Ommaya, A. K., Kaas, J. H., Taub, E., and Mishkin, M. (1991). Massive cortical reorganization after sensory deafferentation in adult macaques. *Science (New York, N.Y.)*, 252(5014):1857–60.

Raffin, E., Mattout, J., Reilly, K. T., and Giraux, P. (2012). Disentangling motor execution from motor imagery with the phantom limb. *Brain*, 135(2):582–595.

Raffin, E., Richard, N., Giraux, P., and Reilly, K. T. (2016). Primary motor cortex changes after amputation correlate with phantom limb pain and the ability to move the phantom limb. *NeuroImage*, 130:134–144.

Ramachandran, V. S. and Hirstein, W. (1998). The perception of phantom limbs. The D. O. Hebb lecture. *Brain*, 121(9):1603–1630.

Ramachandran, V. S. and Rogers-Ramachandran, D. (1996). Synaesthesia in phantom limbs induced with mirrors. *Proceedings of the Royal Society B: Biological Sciences*, 263(1369):377–386.

Rock, I. and Victor, J. (1964). Vision and Touch: An Experimentally Created Conflict between the Two Senses. *Science*, 143(3606):594–596.

Rohde, M., Di Luca, M., and Ernst, M. O. (2011). The Rubber Hand Illusion: Feeling of Ownership and Proprioceptive Drift Do Not Go Hand in Hand. *PLoS ONE*, 6(6):e21659.

Romano, D., Llobera, J., and Blanke, O. (2016). Size and viewpoint of an embodied virtual body affect the processing of painful stimuli. *Journal of Pain*, 17(3):350–358.

Rothgangel, A. S., Braun, S. M., Beurskens, A. J., Seitz, R. J., and Wade, D. T. (2011). The clinical aspects of mirror therapy in rehabilitation. *International Journal of Rehabilitation Research*, 34(1):1–13.

Sakata, H., Takaoka, Y., Kawarasaki, A., and Shibutani, H. (1973). Somatosensory properties of neurons in the superior parietal cortex (area 5) of the rhesus monkey. *Brain Research*, 64(C):85–102.

Saxe, R., Jamal, N., and Powell, L. (2006). My body or yours? The effect of visual perspective on cortical body representations. *Cerebral Cortex*, 16(2):178–182.

Schaefer, M., Flor, H., Heinze, H.-J., and Rotte, M. (2007). Morphing the body: Illusory feeling of an elongated arm affects somatosensory homunculus. *NeuroImage*, 36(3):700–705.

Schaefer, M., Heinze, H.-J., and Rotte, M. (2009). My third arm: Shifts in topography of the somatosensory homunculus predict feeling of an artificial supernumerary arm. *Human Brain Mapping*, 30(5):1413–1420.

Schaefer, M., Konczak, F., Heinze, H.-J., and Rotte, M. (2013). Referral of Touch and Ownership between the Hands and the Role of the Somatosensory Cortices. *PLoS ONE*, 8(1):e52768.

Schmalzl, L. (2011). "Pulling telescoped phantoms out of the stump": Manipulating the perceived position of phantom limbs using a full-body illusion. *Frontiers in Human Neuroscience*, 5(November):1–12.

Schmalzl, L. and Ehrsson, H. H. (2011). Experimental Induction of a Perceived "Telescoped" Limb Using a Full-Body Illusion. *Frontiers in Human Neuroscience*, 5(April):34.

Schmalzl, L., Ragnö, C., and Ehrsson, H. H. (2013). An alternative to traditional mirror therapy: illusory touch can reduce phantom pain when illusory movement does not. *The Clinical journal of pain*, 29(10):e10–8.

Slater, M., Perez-Marcos, D., Ehrsson, H., and Sanchez-Vives, M. V. (2009). Inducing illusory ownership of a virtual body. *Frontiers in Neuroscience*, 3(2):214–220.

Snellen, H. (1862). *Probebuchstaben zur Bestimmung der Sehschärfe*. Van de Weijer, Utrecht.

Synofzik, M., Vosgerau, G., and Newen, A. (2008). Beyond the comparator model: A multifactorial two-step account of agency. *Consciousness and Cognition*, 17(1):219–239.

Taylor-Clarke, M., Kennett, S., Haggard, P., Taylor Clarke, M., Taylor-Clarke, M., Kennett, S., and Haggard, P. (2002). Vision modulates somatosensory cortical processing. *Current Biology*, 12(01):233–236.

Thøgersen, M., Hansen, J., Arendt-Nielsen, L., Flor, H., and Petrini, L. (2018). Removing own-limb visual input using mixed reality (MR) produces a "telescoping" illusion in healthy individuals. *Behavioural Brain Research*, 347:263–271.

Tilak, M., Isaac, S. A., Fletcher, J., Vasanthan, L. T., Subbaiah, R. S., Babu, A., Bhide, R., and Tharion, G. (2016). Mirror Therapy and Transcutaneous Electrical Nerve Stimulation for Management of Phantom Limb Pain in Amputees - A Single Blinded Randomized Controlled Trial. *Physiotherapy Research International*, 21(2):109–115.

Trojan, J., Diers, M., Fuchs, X., Bach, F., Bekrater-Bodmann, R., Foell, J., Kamping, S., Rance, M., Maaß, H., and Flor, H. (2014). An augmented reality home-training system based on the mirror training and imagery approach. *Behavior Research Methods*, 46(3):634–640.

Tsakiris, M. (2010). My body in the brain: A neurocognitive model of body-ownership. *Neuropsychologia*, 48(3):703–712.

Tsakiris, M., Costantini, M., and Haggard, P. (2008). The role of the right temporo-parietal junction in maintaining a coherent sense of one's body. *Neuropsychologia*, 46(12):3014–3018.

Tsakiris, M. and Haggard, P. (2005). The rubber hand illusion revisited: visuotactile integration and self-attribution. *J Exp Psychol Hum Percept Perform*, 31(1):80–91.

Tsakiris, M., Prabhu, G., and Haggard, P. (2006). Having a body versus moving your body: How agency structures body-ownership. *Consciousness and Cognition*, 15(2):423–432.

Tsakiris, M., Schütz-Bosbach, S., and Gallagher, S. (2007). On agency and body-ownership: Phenomenological and neurocognitive reflections. *Consciousness and Cognition*, 16(3):645–660.

Van Den Heiligenberg, F. M., Orlov, T., MacDonald, S. N., Duff, E. P., Henderson Slater, D., Beckmann, C. F., Johansen-Berg, H., Culham, J. C., and Makin, T. R. (2018). Artificial limb representation in amputees. *Brain*, 141(5):1422–1433.

van Koningsbruggen, M. G., Peelen, M. V., and Downing, P. E. (2013). A Causal Role for the Extrastriate Body Area in Detecting People in Real-World Scenes. *Journal of Neuroscience*, 33(16):7003–7010.

Vaso, A., Adahan, H.-M., Gjika, A., Zahaj, S., Zhurda, T., Vyshka, G., and Devor, M. (2014). Peripheral nervous system origin of phantom limb pain. *Pain*, 155(7):1384–1391.

Wake, N., Sano, Y., Oya, R., Sumitani, M., Kumagaya, S.-i., and Kuniyoshi, Y. (2015). Multimodal virtual reality platform for the rehabilitation of phantom limb pain. In *2015 7th International IEEE/EMBS Conference on Neural Engineering (NER)*, volume 2015-July, pages 787–790. IEEE.

Wall, P. D. and Gutnick, M. (1974). Ongoing activity in peripheral nerves: The physiology and pharmacology of impulses originating from a neuroma. *Experimental Neurology*, 43(3):580–593.

Witmer, B. G., Jerome, C. J., and Singer, M. J. (2005). The Factor Structure of the Presence Questionnaire. *Presence: Teleoperators and Virtual Environments*, 14(3):298–312.

SUMMARY

This work concerns a series of three studies investigating how cortical plastic changes and pain processes are affected by changing the body perception through the manipulation of visual feedback in both healthy individuals and amputees with phantom limb pain.

A novel augmented reality platform was created and tested in the initial study. The second study investigated the impact of creating a sensation of a phantom hand in healthy participants by making their hand seem invisible. Participants experienced a shortening of their arm and hand, reminiscent of a phenomenon known as telescoping observed in about 50% of amputees with phantom limbs. Electroencephalography recordings revealed that electrical stimuli applied to the invisible hand was processed differently from both normal vision of the hand and occluded vision of the hand. The third study employed the augmented reality platform in an intervention for amputees with phantom limb pain. The system allowed the amputees to see a virtual visualization of their phantom, overlaid onto the location of the phantom, thereby restoring visual feedback of their missing limb. Following two weeks of intervention, functional magnetic resonance imaging indicated cortical reorganizations and phantom limb pain had decreased by up to 52%.

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