Design and clinical feasibility of an immersive robotic intervention for Phantom Limb Pain

Peter William Snow

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I, Peter William Snow, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

Abstract

Phantom Limb Pain is a common after effect for many traumatic amputees, which in most cases results in chronic life-long pain. Despite the implications of this type of pain, the cause and treatment is not fully understood and ineffective. The use of robotics for the rehabilitation of Phantom Limb Pain capitalises on the ability to map physical movements of the affected limb to a virtual limb. Thus potentially enabling those who cannot be fitted with a prosthetic limb, due to either tissue healing or stump neuromas, to take part in rehabilitation. This in combination with force feedback, immersive virtual reality and muscle control of the affected limb in order to control a virtual avatar provides a platform to study the system's feasibility in treating Phantom Limb Pain and other upper limb conditions with similar pathology. To address this, an immersive robotic system combining virtual reality with robotic movement was developed, facilitating realistic visual and physical interactions enhanced with force feedback to replicate real world physics. A feasibility clinical study was undertaken with 12 upper limb amputees clinically diagnosed with Phantom Limb Pain to evaluate the feasibility of the system as an intervention for Phantom Limb Pain. Participants were assigned to one of two groups. One group experienced immersive virtual reality and the other in addition, the physical properties of the environment. The only difference between the groups was the addition of force feedback, implemented to examine its effects on perceived levels of pain. Participants received nine hours of robotic intervention in total, conducted over a three week period (three hours per week) followed by two follow up questionnaire sessions to determine if any potential pain levels had changed. The primary outcome measure used to assess perceived levels was the clinically validated short McGill Pain questionnaire. Due to the limitations of the study design it was not possible to account for all potential placebo effects which might have influenced the results. However, it is suggested that the paradigm presented in this thesis (with or without force feedback) has the potential to lower perceived levels of pain. In addition the intervention was feasible in a hospital setting, participants were recruited and went through a lengthly protocol with a fully working system which was able to collect data.

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Nomenclature

ADL Activities of Daily Living

CNS Central Nervous System

DOF Degrees of Freedom

EEG Electroencephalography

EMG Electromyography

fMRI Functional Magnetic Resonance Imaging

FSR Force Sensing Resistor

GOD God Object Point

GSR Galvanic Skin Response

HIP Haptic Interaction Point

HMD Head Mounted Display

IK Inverse Kinematics

LDA Linear Discriminant Analysis

MDT Multidisciplinary Team

NHS National Health Service

NS Nervous System

PAD Peripheral Arterial Disease

PLP Phantom Limb Pain

PNS Peripheral Nervous System

RCI Reliable Change Index

RHI Rubber Hand Illusion

RNOH Royal National Orthopaedic Hospital

UE Upper Extremity

UE4 Unreal Engine

V Virtual

VH Virtual and Haptic

VR Virtual Reality

VRPN Virtual-Reality Peripheral Network

Chapter 1

Thesis Introduction

1.1 Problem Statement

Losing a limb through amputation regardless of the cause is a traumatic experience, and as a result all attempts are made to salvage the limb or as much as possible. Regardless there are subsequent problems with rehabilitation including phantom pain and limb non-use, which will effect an amputee's life dramatically [1].

In addition to the physical effects of amputation mental effects both short and long term exist, leading to complex needs and requirements post amputation. These complex needs and requirements also put a strain on rehabilitation resources, involving a range of clinical professionals to ensure that these needs are met, ranging from pain management to living without a limb and providing prosthesis support. The combination of these issues results in the topic of amputation and post amputation care involving interdisciplinary ongoing research subjects, directly affecting the lives of those suffering post amputation.

The PhD was funded by the Defence Science and Technology Lab (Dstl), which in recent years has funded research related to amputation due to the Afghanistan and Iraq campaigns [2][3]. This has lead to a growth in research focusing on improving limb salvage via medical procedures and post amputation aspects such as prosthesis design and rehabilitation. Although this surge in development is based on military funding, the effects are now being transferred to civilian use in the UK via the NHS. This coupled with technical advancements and reduced cost of sensors, computing and robotics creates avenues of research that weren't possible even a decade ago.

Phantom limb pain affects the majority of amputees (50-80%) and results in the sensation that body parts which are no longer there being present [4]. Amputated limbs can ache, itch, burn, feel dry or wet, tense, locked or stuck, or even feel like they are moving. They may be described as feeling that the missing body part is "positioned awkwardly or painfully".

The pain usually develops in the first couple months after amputation and is most likely to develop in individuals who lost their limb/s painfully as a result of accident, explosion, shooting etc [5]. The effects of phantom limb pain can be exacerbated due to anxiety/stress and other factors [6]. This can affect the individual's mental state and their physical state via potentially reduced engagement with their rehabilitation.

As further discussed in the thesis in chapter 5, a range of options are available from pharmacological interventions to further surgery. Issues with these type of treatments and non invasive treatments vary, partly due to the individuality of the amputee and their injuries and subsequent auxiliary injuries such as brachial plexus and stump neuromas. Each of these injuries causes issues with amputees using non invasive treatments such as using a prosthesis due to stump neuromas. One area of treatment that has been shown to decrease pain, however varies in effectiveness is that of Ramachandran's mirror box therapy [7]. Enabling those who due to stump neuromas and additional injuries who are unable to wear a prosthesis to take part in rehabilitation due to its non invasive nature, and is used as a basis for this research.

Some modern systems have utilised virtual reality to act as an immersive mirror box therapy paradigm [8] however the work detailed in this thesis is the first to combine virtual reality and force feedback through haptic robotics, in order to examine its effect on Phantom Limb Pain via a feasibility clinical study. The use of virtual reality and rehabilitation robotics allows those who cannot wear a prosthesis (due to early stages of tissue healing or other further complications such as stump neuromas) to take part in rehabilitation through realistic simulation of activities of the daily living. Through the immersive visual component, it is possible to tailor the exercises to the individual's constraints (e.g. scaling virtual movement). It could also potentially be used to provide early training of how to use a prosthesis by those who are going through the tissue healing stages through simulation of the prosthesis function and its dynamics.

Previous research have fallen short in obtaining effective results [8][9], mainly focusing on converting Ramachandran's mirror box therapy either directly to virtual reality or adding in basic EMG systems to allow simple myoelectric control rather than focusing on adding movement of the amputated limb in conjunction with using residual muscles to open and close a virtual hand to manipulate objects within a virtual environment. What is missing

from previous research is the element of enhancing the visual illusion with force feedback along with engaging in actual movement and opening/closing a hand via EMG sensors as opposed to imaginary movements.

The aim of this thesis is to see if the effect of adding haptics via force feedback on an immersive virtual reality system acting as a decoupled (allowing movement of the affected arm to be made from the affected arm not the intact arm) mirror box therapy paradigm, has clinically significant impact on perceived pain levels.

In order to test out the effectiveness of the system, a feasibility clinical study was conducted examining the effects that force feedback had on perceived pain levels. The feasibility clinical study involved two groups of six upper limb amputees suffering from Phantom Limb Pain.

Both groups experienced the same system, but with one group also feeling force feedback interactions. Pain levels were recorded on baseline measurements, with levels being recorded at the end of every session. Participants received nine hours of intervention in total, conducted over a three-week period (three hours per week) followed by two follow up sessions to determine if any potential pain levels had changed. In addition, further measures were taken such as an embodiment questionnaire (used to see if the participant believed that the virtual limb was theirs) to examine any links between embodiment and pain.

The research carried out as part of the PhD builds on the reported literature and on experience in developing and applying haptic/robotic principles to the delivery of therapies to patients following a brain injury and/or other cognitive deficits relating to movement disorders. The research aims to expand on work using robotics for rehabilitation following similar injuries which has been shown to have a positive effect on neural plasticity through interactive sensorimotor exercises.

1.2 Objectives and Hypothesis

1.2.1 Objectives

1. To develop an immersive virtual reality and haptic robotic system that allows upper limb amputees to take part in exercises that involve: i) movement of the affected limb tracked by the robot; ii) classified muscle activity from the affected limb to open and

close a virtual hand that would allow reach, grasp, transport and release of objects; iii) provide force feedback when manipulating objects in the virtual environment (e.g. feel object physical properties such as geometry, weight, friction, collisions) to mimic real physical interactions.

2. Carry out a feasibility clinical study with a cohort of upper limb amputees who are clinically diagnosed with Phantom Limb Pain to examine the feasibility of its use in a clinical setting and its effect on pain.

1.2.2 Hypothesis

That providing force feedback through a haptic interface that can move in three-dimensional space in conjunction with a visual surrogate for the missing limb while interacting with a virtual object in an immersive virtual reality environment, will enhance embodiment and agency and result in a higher reduction of perceived pain than with a visual surrogate without force feedback.

This hypothesis is based on the concept that humans interact and perceive the environment within an action space where the humans' possibilities for action will affect perception. Thus, by enhancing perception within the action space, it results in changed perception in amputees.

To test the hypothesis the research presented in this thesis evaluates the effect of immersive virtual haptic therapies on perceived pain using the short McGill pain questionnaire as the primary outcome measure. Participants engage with the system developed by providing direct physical contact with a haptic device, mapping of the information from the device to the virtual representation of the physical limb and exercise involving simple repetitive movements that maintains challenge and interest to the individual.

1.3 Thesis Outline

The thesis is broken into five parts making ten chapters as shown in Figure 1.1.

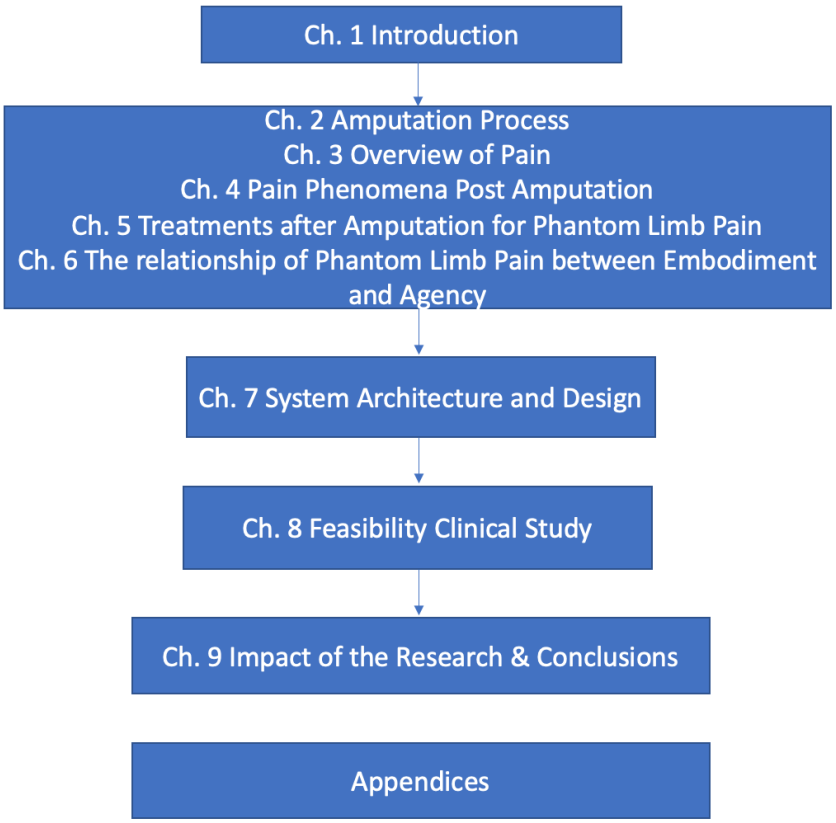


Figure 1.1: Flow chart showing the chapters sectioned into their respective areas, together with Appendices which contain additional technical information.

Chapter 1 introduces the thesis structure, the PhD's hypothesis, aims and objectives, providing an overview which backs up the results found in chapter 10.

The next block of chapters 2 to 6 present the literature review and background of pain, amputation, pain phenomena during the amputation process, previous and current treatments for Phantom Limb Pain, and both Embodiment and agency and how it relates to Phantom Limb Pain.

Chapter 2 presents the process involving amputation, as well as highlighting the post amputation long term elements. This chapter provides an overview of the amputation process, emphasising that the amputation itself is the start of a journey which ranges from initial rehabilitation to managing pain.

Chapter 3 provides a general overview of pain, it's mechanisms along with acute and chronic pain.

Chapter 4 looks at the different pain phenomena during the amputation process expanding chapters 2 and 3. This chapter examines Phantom Limb Pain but also lays a foundation on which therapies have been developed to help treat sufferers. In addition to highlighting the

complexities involved in its mechanisms which make developing such therapies complex.

Chapter 5 focuses on traditional and technological treatments for Phantom Limb Pain, examining the effectiveness of these treatments and highlighting gaps in technological treatments which the research presented in this thesis includes. This chapter underlines the shortcomings in traditional methods and technologies for treating Phantom Limb Pain. These shortcomings stem from the complexities of Phantom Limb Pain examined in chapter 4. This chapter also stresses gaps in the research which the thesis addresses.

Finally in this block chapter 6 looks at embodiment and agency, elements highlighted in chapter 5 as potential non invasive treatments for Phantom Limb Pain, such as the use of mirror box therapy. Embodiment and agency are concepts that technological treatments for Phantom Limb Pain take as a foundation.

The overview and detailed elements of the system are presented in chapter 7.

Chapter 7 provides an overview of the architecture in terms of software and hardware used in the system developed for the PhD. This chapter looks at the user and technical requirements taken into consideration when designing the system, following consultation with the clinical collaborators and user groups through the prosthetics and orthotics unit, RNOH. The system underwent several design revisions/iterations before arriving at the system presented in the chapter, which can be can reconfigurable to the individual participants needs. Along with the system architecture, examining components such as human responses, sensors, models and multi-modal controllers which make up the system were in depth examination of elements such as interactions which take place between these components. The design draws on gaps within previous research in order to examine the effects of a force feedback and immersive virtual reality paradigm in order to alleviate Phantom Limb Pain.

Next the feasibility clinical study is detailed with the results discussed in chapter 8, with the first part of the chapter, explaining the methodology of the study, highlighting objectives, measures, design, participants and recruitment and data collection.

The rest of the chapter provides an overview of the results. The designed system was able to deliver therapy, however ongoing uncertainty over the mechanisms surrounding Phantom Limb Pain coupled with issues with the study design in terms of placebo effects, warrant further more rigorously designed studies in the future.

Chapter 9 wraps up the thesis, examining the impact and final conclusions to the PhD, discussing the contributions this thesis provides to Phantom Limb Pain, its treatment and lessons learnt from the research leading to future work.

The appendices contain previous submitted papers/posters together with paperwork associated with the ethics approvals and participant data.

Chapter 2

Amputation Process

2.1 Introduction

Amputation is a surgical procedure that results in the removal of an extremity or in the removal of a partial or complete limb. It can be due to injury, frostbite, disease such as diabetes [10] as well as infection and cancer. Recent conflicts and civilian statistics have shown that lower limb amputation is twice as common than upper limb amputation [11], however this has been suggested to be the case in higher income countries [12]. The effects of upper limb amputation suggest more severe impairments as a result of the reduced mobility and lower quality of life. Studies of the amputee population from a military background has shown that such amputations mainly affect younger age groups [13][5]. One important factor in the amputation process is that the rehabilitation phase is a lifelong effort and doesn't end with the amputee finishing the initial rehabilitation phase [14].

This chapter will examine the overview of the amputation procedure highlighting elements which need to be taken into consideration when designing the system as part of the PhD.

2.1.1 Reasons for carrying out the amputation

In a military setting study Clouse and colleagues suggest [11] that the majority (65%) of injuries which result in amputation of the upper extremity's (UE) were caused by improvised explosive devices. However this data does not cover civilian populations. The number of injuries from improvised explosive devices is the main cause of wounding in combat related injuries in recent years [15] and although limb salvage rates have risen [11] the methods and procedures of amputee care carry on being refined and improved [15]. Statistics from the UN suggest that from 2009-2021, 35899 civilian casualties have occurred, with 49% in 2021 being related to explosion injuries [16]. Despite the difficult nature of reporting casualty figures from war-zones these numbers of civilian casualties are significantly higher than

combat troop casualties (UK numbers from 2002 - 2014) at 616 casualties[17]. Focusing on upper limb amputation, the main types of amputations carried out are the following [18]:

- upper digit amputation, where the thumb or one or more of the fingers are amputated;
- transhumeral, where the hand and a section of the arm are amputated above the elbow;
- transradial, where the hand and a section of the arm are amputated below the elbow;
- partial hand amputation, where a section of the hand is amputated;
- shoulder disarticulation, where the amputation occurs through the shoulder joint, removing the entire arm;
- double upper amputations, where both hands and some of the arms are amputated;
- forequarter amputation, where the entire arm is amputated along with a section of the shoulder blade and collar bone;
- wrist disarticulation, where the amputation occurs through the wrist joint, removing the hand;
- elbow disarticulation, where the amputation occurs through the elbow joint, removing the hand, wrist and forearm.

The above list is ordered by the number that are performed in the UK by the NHS. Unlike lower limb amputation, most upper limb amputation is carried out due to traumatic injury [18]. 70% of patients with upper limb loss undergo amputation below the elbow.

2.1.2 Amputation risks

In the event that limb salvage is not feasible amputation must proceed with varying patient specific risks. A common risk found in both civilian and military amputations is that of infection. A major risk of infection from a combat related amputation comes from the environmental properties such as dirt around the patient at the time of injury [19]. These risks can cause complications during the amputation such as: heart complications, blood clots (venous thrombosis), infection at the site of the surgery, pneumonia and further surgery being required as a result of the mentioned complications [18]. As a result, these factors have to be taken into consideration during the course of the amputation procedure.

2.1.3 Procedure before amputation

Due to the complex nature of the amputation procedure a varied number of health professionals are included in what is called multidisciplinary teams (MDTs). In a civilian context this team includes: a surgeon, a nurse specialising in pain relief, a psychologist, a social worker, a pharmacist, a prosthetist, a dietician, a physiotherapist and an occupational therapist [20].

The procedure for a civilian and a combat related amputation differs according to the situation. A civilian amputation unless carried out in an emergency involves pre- operative assessments such as, tests and procedures to determine the type of amputation and issues which might affect the rehabilitation post amputation, like medical examinations, assessment of the healthy limb and psychological assessments [20]. One important assessment often included in this phase is the introduction of a physiotherapist and prosthetist. The role of the prosthetist before amputation is to provide a realistic expectations of prosthesis to take measurements and a plaster cast of the remaining limb to start fabrication of the prosthesis [21]. Factors which affect what kind of prosthesis can be used include: the type of amputation, muscle strength in remaining sections of the amputated limb, expected tasks to be performed after the amputation and whether the limb should look as physically real as possible. Prostheses which look as real as possible to the intact arm have traditionally lacked functions being mainly for cosmetic purposes[20]. In a situation of a war wound, a traumatic amputation resulting from ballistic or explosive injuries, does not undergo the procedures mentioned above and therefore the decision to amputate is taken at the time of the wound assessment [22]. Unlike civilian non-traumatic cases, many war injuries are often heavily contaminated due to the improvised explosive devices and the environment. Consequently the primary treatment of such injuries has to be carried out as soon as possible to keep complications to a minimum [23]. There are two types of explosions that can cause injury. In explosions from conventional bombs, a shock wave of high pressure is followed by a blast wind or air in motion, on the other hand, enhanced-blast explosive devices trigger a primary blast that is followed by a secondary explosion [24]. Both of these types of explosions can lead to injuries categorised into 4 groups [5][24]:

- Primary - patients close to the centre of the explosion have damage to air filled cavities. E.g. lungs, middle ear and the bowel. Immediate effects of primary

explosions are direct effects (overpressurisation and underpressurisation), rupture of tympanic membranes, hollow viscera and also pulmonary damage.

- Secondary - injuries sustained due to impact from items energised by the explosions, e.g. preformed metallic fragments. Immediate effects of secondary explosions are penetrating trauma and fragmentation injuries.
- Tertiary - injuries sustained when a patient is accelerated against fixed objects such as walls. As a result the immediate effects of tertiary explosions can cause crush injures, blunt trauma, penetrating trauma, fractures, instantaneous traumatic amputations and open or closed brain injuries.
- Quaternary - injuries sustained as a result of the effects of the explosions, e.g. burns, asphyxia, exposure to toxic inhalants and injuries caused by the structural effects of the explosion, like the collapse of the building which the explosion has taken place.

Noteworthy, patients with secondary, tertiary and quaternary type injuries could acquire sufficient limb damage to warrant an amputation even if the injuries at the time of damage do not warrant amputation.

2.1.4 Procedure during amputation

Despite the differences in the causes that lead to an amputation within a civilian or military setting the procedure of amputation regardless is quite similar. However the following section describes the procedure of a war wound amputation in line with this thesis's context [20][22].

- Amputation is carried out under a general or spinal anaesthesia, administered before the procedure, and always under tourniquet to prevent further damage and blood loss.
- Dead and contaminated tissue is excised in a procedure called debridement, in combination with antibiotics to minimise infection rates.
- The limb to be amputated is assessed to determine the level of amputation, to preserve the best functional level for the limb post amputation.
- The amputation is carried out on the limb, traditionally performed as a guillotine amputation, transecting skin, muscle and bone all at the same time.
- After the amputation has been performed the surgeon fashions flaps using the myoplastic technique, this is, the muscle is sutured and then placed over the end

of the bone before closing the wound. In turn it helps to produce active muscles, restoring their function even at the stump end region, and brings arterial and venous circulation back to normal [25]. This enables the stump to be shaped in such a way that it is smooth and has a regular contour to facilitate prosthesis use by ensuring that the stump is covered by skin and maximising the stump's strength [26].

- The wound is left open and dressed with dry, bulky, dressing until delayed primary closure.

Although the above list details the traditional approach to amputation, recent advances in the field have produced further techniques such as Microsurgery (which has the capability to potentially save damaged limbs), Re-implantation (if certain conditions are met the limb can be reattached), Limb transplantation (not widely used, due to the lack of suitable donors and rejection rates) and Osseointegration (a technique whereby an anchor for a prosthesis is inserted into the bone allowing skin to grow around the newly attached anchor). After surgery the patient remains in hospital or in a war setting amputation, the patient is transported to another hospital whereby the next phase begins, rehabilitation.

2.1.5 Procedure after amputation - hospital, home and long term care

After the surgery and the initial recovery from the amputation, the wound and stump is monitored very carefully to avoid any possible complications [27]. Once the effects of the surgery have subsided the next phase of the process is rehabilitation. The main goal of rehabilitation is the "enhancement and preservation of function" [28] which is achieved by [5][28]:

- minimising the functional decline associated with the illness or injury, by reducing swelling and prevent contractures.
- preventing additional disability during the acute care episode.
- shortening the time course of recovery.

The rehabilitation phase is supported by a range of clinical professionals and requires lifelong attention and adjustment across a range of clinics and outpatient sessions [23]. This period post amputation, is important to this thesis's research since procedures such as prosthesis fitting and learning are undertaken initially within this period.

2.2 Impact on this research project

Due to the traumatic nature of amputations the initial procedure is critical, the quality of the surgery along with the length of the remaining amputated arm and any surrounding damage greatly impacts the amputee's process.

Not only does the initial amputation affect the rehabilitation of the amputee but also significantly plays a part in determining what short and long term pain an amputee is likely to face (discussed in section 4.2 chapter 4) from stump pain to long term issues of stump neuromas.

A system which can be used in the early stages post amputation could mitigate any issues at this stage of the rehabilitation process which could reduce a range of short and long term pain conditions mentioned in the next two chapters.

2.3 Summary

This chapter has looked at the amputation processes associated pre, during and after amputation. It discussed the reasons why amputation is carried out, the risks involved with the amputation and provided an overview of the rehabilitation phases. The next two chapters examine the pain post amputation and provide an overview of pain in general is provided before an in-depth discussion of pain suffered by amputees post amputation.

Chapter 3

Overview of Pain

3.1 Introduction

The following chapter looks at the specifics of pain as experienced by those who have had an amputation. This chapter aims is aimed at providing a foundation in pain from a neurological perspective. [1].

3.2 General Overview of Pain

3.2.1 General organisation of the nervous system

The nervous system (NS) (Figure 3.1) refers to the network of both nerves and cells (neurons) as a whole, which is responsible for communicating messages between the brain and spinal cord and various systems around the body. The Peripheral nervous system (PNS) and the Central nervous system (CNS) are the two major parts of the human nervous system. The PNS is divided in autonomic and somatic NS, the brain and the spinal cord compose the CNS. The sympathetic and the parasympathetic nervous systems constitute the autonomic NS [29].

[1] Readers with a general understanding of the neurological background of pain might wish to continue at chapter

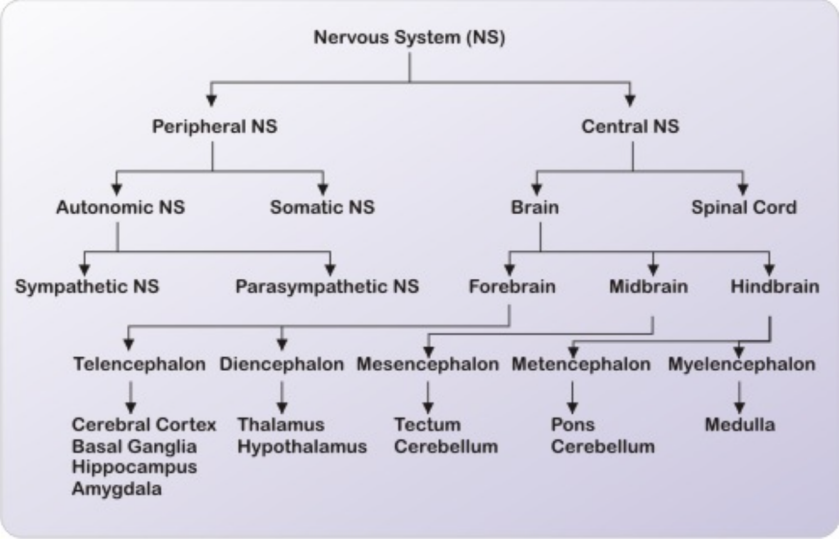


Figure 3.1: Organisation of the human nervous system. Showing the divisions of Peripheral and Central Nervous Systems and their sub systems anatomically grouped. Extrapolated from [30]

Figure 3.1 shows the hierarchy of the NS structures to the subsequent systems, in the body both the CNS and PNS communicate information between each other as one system. Figure 3.2 demonstrates this by showing the anatomic structure of the nervous system. Sensory and motor areas of the brain (cortex) have also been mapped to different body parts according to their movement and sensory complexity as represented by Penfield's homunculus (Figure 3.3) suggesting proportions of the human brain devoted to processing motor or sensory functions for different parts of the body shown on the diagram, with the arms and hands functions taking up considerable parts of the brain stressing their importance. The CNS works in synchrony with the PNS to control voluntary and involuntary movement execution. In addition to generating and controlling involuntary movements the CNS is also responsible for planning and correcting movement. It has been hypothesised that the motor planning and execution process makes use of internal models driving sensorimotor integration using feedback and feedforward mechanisms to act as predictors in the absence of visual feedback [3].

The organisation of the nervous system is demonstrated in Figure 3-2, however an in depth review is needed to understand the sub systems involved, and how they facilitate movement and sensation.

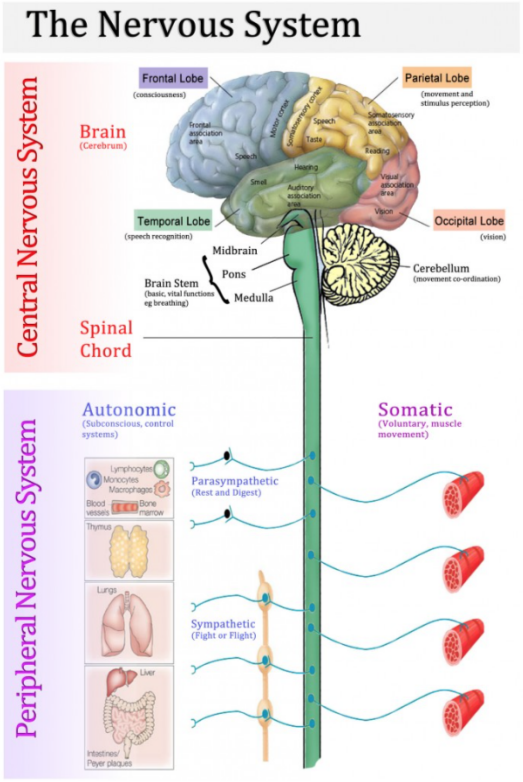


Figure 3.2: Anatomic representation of the nervous system, showing the separated area of the CNS and PNS. Extracted from [31]

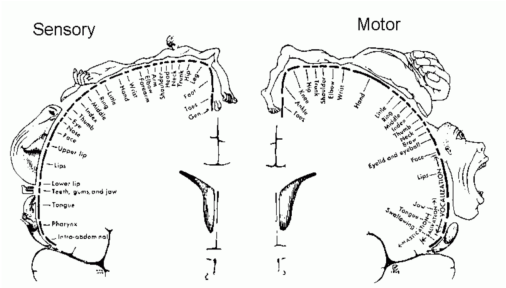


Figure 3.3: Penfield's homunculus, showing the cortical mapping between the sensory and motor systems exhibited in the nervous system. Adapted from [32]

3.2.2 Pain

Pain can be described as a complex multisystem output that is computed by the brain, in response to an event such as a possible threat. Immediate response systems in the PNS are regulated by integrated multi-system responses, such as chemicals released by the inflammatory system with onset damage, which form part of the physical process leading to healing of tissue [33]. Pain can either be acute or chronic and is described in the following sections.

3.2.3 Acute Pain

Instant and short-term pain, which is experienced for less than twelve weeks duration is described as acute pain [34][35]. Nociception, as first described by Sherrington in 1906 [36], forms the basis for pain perception. It describes the overall process in which the noxious stimulus, either external or internal, can cause damage to the tissue and trigger a response that is neurologically communicated from the source of stimulation to the Central Nervous System via free nerve endings. This process is broken down into four distinct sub steps: transduction, transmission, perception and modulation pain phases [37].

3.2.3.1 Transduction of pain phase

The transduction pain phase is initiated when primary sensory neurons (nociceptors) detect intense mechanical, chemical or thermal stimuli, thus this phase acts as the first defence mechanism in maintaining the body's integrity [38]. Nociceptor neurons have cell bodies located in the dorsal root ganglia of peripheral nerves inside the spine and transmit via peripheral sensory nerves. These neurons, as opposed to normal sensory neurons, are lightly or non-myelinated and can be found in somatic cells. Furthermore, they can be found in somatic cells for example in tissue, bones and skin, also in visceral organs such as the lung and heart. In addition these cells are found in neuron located at the axon end where A-delta and C fibres are located which are involved in the transmission of pain. Of relevance to the PhD's work is the different types of pain quality that relates to these two fibers. The A-delta fibers are present in the skin and are activated by cutaneous stimulation, which result in faster conduction of pain, therefore also associated with "first pain". These fibers are responsible for the localised, sharp, stinging and pricking pain. On the other hand, the "second pain" is associated with the C fibers, which are slow conducting fibers that transmit dull, burning or aching pain generally diffusing over a wider area. These pain sensations are relevant because they demonstrate the types of pain experienced by Phantom Limb Pain sufferers [39].

3.2.3.2 Transmission of pain phase

Once the transduction phase is completed the pain impulses are transmitted to the brain [40] (Figure 3.4). This is achieved through the following steps:

1. Pain impulses originating at the transduction location are transmitted along the fibers

to the spinal cord.

2. Next, the pain impulses are conducted from the spinal cord to the brain stem.

3. Lastly, the pain impulses travel through the other neurological connections including the cortex, and subsequently to the higher cognitive levels of the brain [41].

During the transmission phase the pain impulses are transmitted from the spinal cord to the brain stem and subsequent areas of the brain, such as the thalamus via two main nociceptive ascending pathways: the spinothalamic and the spinoparabrachial pathway [42]. These two pathways form the anterolateral system. The ascending and descending pathways are discussed in sections 3.2.4. Figure 3.5 [33] demonstrates the possible transmission phase pathways involved in the transmission of the pain stimuli from the spinal cord to the brain as well as other systems affected and the responses from those systems. Figure 3.5 shows the transmission of pain from the sensory input to the brain via the spinal cord similar to Figure 3.4 but in more detail including the outcomes of pain "heightened evaluation of threat, fear and social responses" and behavioural changes such as "protect, immobilise, medicate and seek treatment".

3.2.3.3 Perception of pain phase

The perception of pain is initiated when the transmission phase is completed and the brain interprets the incoming nervous messages. The ultimate physical reaction then becomes a conscious multifaceted experience as it is influenced by affective- motivational, sensory-discriminative, emotional and behavioural elements. These elements play an important role in understanding the outcomes of pain mentally. When the stimuli are transmitted from the brain stem up to the thalamus during Nociception, multiple cortical areas within the brain are triggered and responses are generated. These areas are [43][44][45]:

- The reticular system: is responsible for the autonomic and motor response (reflex) to pain and for signalling the body to take action, e.g. automatically reflexing a hand away when a knife cuts into it. This system is also involved in the affective-motivational response to pain stimuli, such as surveying and assessing the physical injury to the hand once a knife has been moved away. This response will then trigger

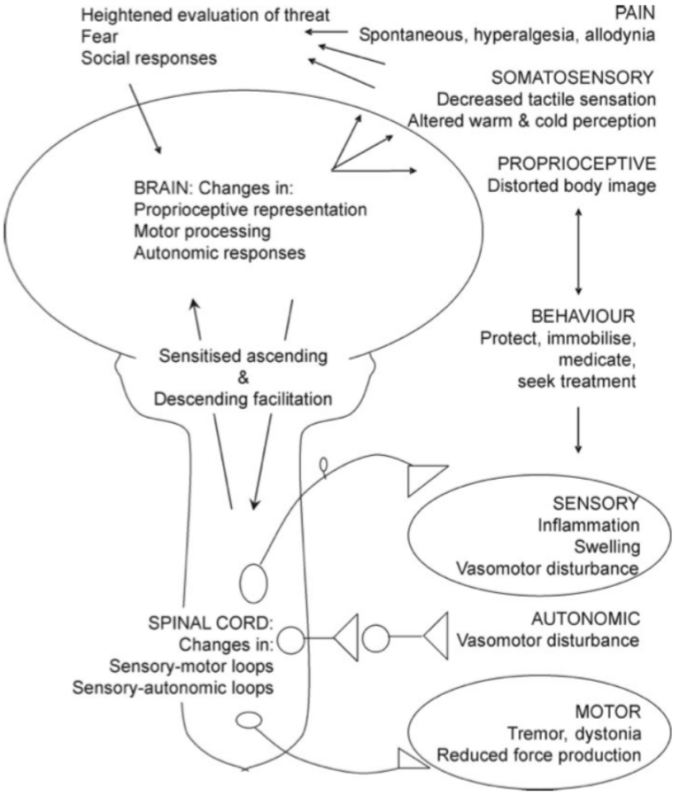


Figure 3.4: Pathway and systems of the transmission of pain phase. Diagram extracted from [33]

the suitable action plan for dealing with the pain e.g. taking medical steps to tend to the wound.

- Somatosensory cortex: is responsible for the perception and interpretation of sensations felt by the body, in this case via the nociceptors. This area classifies the intensity, type and physical location of the pain sensation and links it to past memory (experiences) and cognitive activities. The Somatosensory cortex also classifies the various attributes of the stimuli before it triggers responses, e.g. where the pain stimulus is, the intensity of the pain stimulus and what the stimulus feels like (such as sharp stabbing pain and burning sensation for example) depending on the current situation.

- Limbic system: in the context of pain, it is responsible for the emotional and behavioural responses to the pain stimuli, for example the current state of attention at the time, mood and motivation. The Limbic system is similar in some respect to the Somatosensory cortex as it also associates the stimuli to past experiences of pain and how that pain was processed.

3.2.3.4 Modulation of pain phase

The last phase in Nociception is the modulation of pain. It comprises of changing or inhibiting transmission of pain impulses in the spinal cord. The multiple and complex pathways involved in this phase are related to the modulation of pain and are referred to as the descending modulatory pain pathways (DMPP). Additionally, they can lead to either an increase or a decrease in the transmission of pain impulses; this is the excitatory or inhibition transmission, respectively [46]. Descending inhibition involves the release of inhibitory neurotransmitters that fully or partially block the transmission of pain impulses, and therefore produce analgesia [47]. Inhibitory neurotransmitters involved with the modulation of pain include: endogenous opioids (enkephalins and endorphins), serotonin (5-HT), norepinephirine (noradrenalin), gamma-aminobutyric acid (GABA), neurotensin, acetylcholine and oxytocin [48][49][50][51]. Endogenous pain modulation helps to explain the wide variations in the perception of pain in different people as individuals produce different amounts of inhibitory neurotransmitters.

3.2.4 Descending pathways of pain

As mentioned in the previous section, there are ascending pain pathways from the stimuli to the brain as well as descending pain pathways communicating from the brain to the rest of the body aiming to inhibit pain. The descending pathways begin in the periaqueductal gray (PAG) area, whose projections lead to the rostral ventromedial medulla (RVM) and spinal cord dorsal horn [52]. Stimulation of the PAG has been shown to produce analgesia, but no change in the ability to detect temperature, pressure, or touch [53]. The neurons beginning in the PAG end on cells in the medulla, including the serotonergic cell bodies of the raphe nuclei. The serotonergic neurons then descend into the spinal cord to inhibit cell firing. Other cells in the PAG terminate close to the locus coeruleus in the brainstem. Accordingly, there are at least two major pathways that descend to the spinal cord to inhibit the projection of pain. This can be demonstrated in Figure 3.5 [54].

3.2.5 Chronic Pain

Chronic pain can be a major problem for some patients impacting on their quality of life [4]. It can be caused by reorganisation of nociception by injury as in the case of disease,

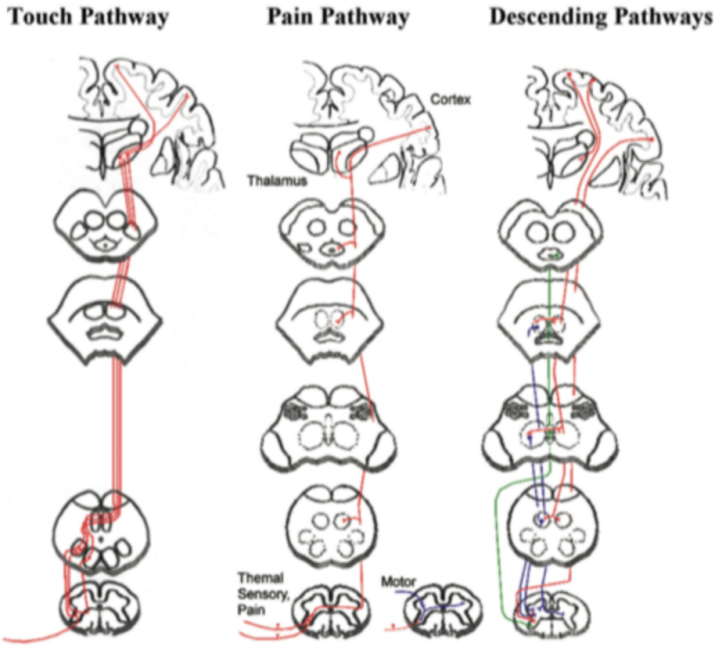


Figure 3.5: Ascending and descending pain pathways and the touch pathway. Diagram extracted from [54]

such as cancer, and it can also occur from present or past damage to the PNS, the CNS, or as in Phantom Limb Pain a combination of physical and mental conditions.

3.2.5.1 Pathophysiology of chronic pain

Due to the range of chronic pain and the situations that can give rise to it, there are numerous mechanisms involved in the pathophysiology of chronic pain and these have not been fully explored. Some studies [55] have stated that following injury, rapid and long-term changes occur in parts of the CNS that are involved in the transmission and modulation of pain and the nociceptive information, thus leading to chronic pain. The spinal cord exhibits a core mechanism called "wind-up" also referred to as hypersensitivity or hyperexcitability. Wind-up occurs when repeated, prolonged, noxious stimulation causes the dorsal horn neurons to transmit progressively increasing numbers of pain impulses [56]. Some patients can experience extreme pain in response to stimuli that in a normal context is not thought of as painful, such as touch or brushing, as well as thermal skin conditions. This is known as allodynia and it is relevant when examined in conjunction with Phantom Limb Pain [57]. Allodynia associated with upper limb syndromes have also been documented as chronic pain [58][59]. This abnormal processing of pain within the PNS and CNS may become detached in a painful event.

3.2.5.2 Neuropathic pain

Also associated with chronic pain is neuropathic pain, which can be defined as pain emerged or caused by a primary lesion or abnormality in the nervous system resulting from various causes. Trauma as chronic post-surgical pain; infection as a possible outcome of surgery but not exclusive to surgery can all contribute to neuropathic pain [60]. Some types of neuropathic pain may develop when the PNS has become damaged, causing the pain fibers to transmit pain impulses repetitively and become increasingly sensitive to pain stimuli. Neuropathic pain is distinctly different from nociceptive pain and can be described as burning, dull, aching, tingling, and electric shock. These characteristics are all common to the pain experienced by sufferers of Phantom Limb Pain [57].

3.3 Summary

Chapter 3 has provided an overview of pain from a neurological perspective from the organisation of the nervous system, a key part of the pain process in terms of transduction and transmission of pain to describing both acute and chronic pain.

By providing this overview, one can gain an appreciation of the complexities surrounding even the basics of pain. As the next chapter will show this is further compounded when an amputation is performed, as highlighted by the pervious chapter, including areas not widely researched which is related to the amputee population, and in particular different pain phenomena experienced after the amputation process.

Chapter 4

Pain Phenomena Post Amputation

4.1 Introduction

Due to the number and complexity of the regions involved in amputation which include peripheral, spinal and cortical areas a number of different forms of pain can occur. Consequently, a number of pain phenomena can arise post amputation. A review of pain after amputation in 2016 by Neil [30] details not just Phantom Limb Pain but also Stump pain and even back pain due to adapting to life with a missing limb. This combination of pain phenomena causes far reaching implications for the amputee. A study 50+ years post World War 2 found that 55% of amputees whose amputation occurred during the war questioned still suffered from Phantom Limb Pain and 56% respondents still suffered from stump pain [61]. Below is an overview of stump pain, back pain resulting from amputation along with a detailed examination of Phantom Limb Phenomenon, Sensation and Pain.

4.2 Different Pain Phenomena experienced during the amputation process

4.2.1 Stump Pain following amputation

Following initial surgery, wound pain is common due to tissue damage from an incision and associated actions afterwards such as closing the incision and applying pressure during surgery [62] which lasts a few days before stump pain develops, also called residual limb pain. A 1984 study on phantom and stump pain on a military population suggested the incidence of stump pain at 62% [63] with a more recent study in 2004 suggesting the number was between 13-71% of the amputee population [64]. Jensen et al in 1985 examined stump pain over a time of two years with a population of 58 amputees. Their findings suggested that shortly after amputation (8 days) 57% of the population experienced stump

pain, dropping to 22% after 6 months and by the end of the two years only 10% experienced stump pain [65]. One suggestion to this could be due to the difficulty of determining if the pain is stump pain or phantom limb pain. Stump pain cause the amputee discomfort and associated causes can lead to reduced rehabilitation outcomes and quality of life [66].

Surgical stump pain is a combination of nociceptive and neuropathic pain due to tissue damage and resulting neural injury at the site of amputation [30], being described as severe with burning/tingling sensations [67] at the site of amputation. These pain sensations are similar to Phantom Limb Pain in severity however Phantom Limb Pain is not found at the site of amputation but typically at the distal extremes of the missing limb [30].

This acute phase of stump pain generally resolves itself after a few weeks post amputation, however around 10% of amputees will continue to experience stump pain which leads to chronic/persistent stump pain [68]. The causes of chronic/persistent stump pain are summarised below[30].

- Infection
- Stump Neuroma
- Heterotopic Ossification
- Wound Breakdown
- Arterial Insufficiency
- Osteomyelitis
- Bone Spur
- Haematoma
- Insufficient Myoplasty Covering
- Poorly fitted Prosthesis

Infection of the stump post amputation is relatively common with higher rates seen in lower limb below the knee [69]. Of more concern than infection post amputation for upper limb amputees is that of acute limb ischemia [70] and stump neuromas, although infection of the stump is still a concern for both upper and lower amputee. Higher levels of infection are found in populations with pre-existing conditions such as diabetes, pre-existing infection before amputation and vascular compromise [30]. In extreme cases this can lead to further re-amputation and subsequent complications. As a result infections need to be kept to a

minimum and if diagnosed must be treated quickly.

Stump Neuroma is the result of the inflammatory reaction once a nerve has been severed. The nerve begins to regenerate toward its distal part of the limb in the case of an amputation. If during the regeneration the growth is disorganised or incomplete, the possibility of the formation of a neuroma or a growth or tumour may occur [71]. The neuroma takes on the form of a bundle of nerves which leads to reduced nerve activation in the effected area of the stump and non-provoked pain around the area of the neuroma. Numerous treatments for neuromas exist both surgical and non surgical, however non surgical methods have yielded unsatisfactory results, with surgical methods of treatment preferred including extracting the neuroma [71]. However these methods can also lead to further neuromas at the site of extraction.

Stump neuromas affect up to 48.7% of amputees[72] and "result in intractable pain, inability to wear a prosthetic device, and lost work"[73]. Of interest is research suggesting that there is a close association between the presence and severity of stump neuroma pain and phantom limb pain [30]. This raises issues regarding treatment of stump neuromas in addition to Phantom Limb Pain due to around 50% of amputees suffering from neuromas. As highlighted by Watson and colleagues "Some initial methods of treatment include physical therapy, desensitization, and pain medication. Oral pharmacological treatment with drugs such as gabapentin or pregabalin is sometimes used. If there has not been a useful response in 6 months, it is unlikely to occur, and surgical treatments must be considered"[74]. In order for the amputee to perform physical therapy in such a way in order to maximise their chances of a response within 6 months and avoid further surgical intervention, robotic therapy could potentially meet this challenge in lieu of any inability of the amputee to wear a prosthetic device.

Heterotopic Ossification is an uncommon phenomenon in the majority of amputees however in recent years due to conflicts and traumatic, combat related amputations has lead to a sharp rise in amputees with this phenomenon [75]. Heterotopic Ossification is the process of formation of extraskeletal bone in muscle and soft tissues in the amputated stump's soft tissue. Amputees who suffer from heterotopic ossification experience pain and also skin breakdown around the effected area and difficulties both fitting a prosthetic limb and using a prosthetic limb [75]. The prevalence of this in traumatic amputees in a study by Potter et al has been found to be as high as 63% [75] with head trauma shown

to increase the chances of heterotopic ossification. The calcium build up leads to the formation of bone in the soft tissue [76] which presents further problems including potential re-amputation. The use of pharmacological intervention has been shown to lack evidence in treating heterotopic ossification in amputees [30].

One of the four risk factors for developing phantom limb pain is the presence of persistent stump pain [64] highlighting the importance in treating stump pain as a priority. With the majority of amputees at least experiencing acute short term stump pain the issues surrounding stump pain must be addressed in order to help avoid knock on effects. This element also adds to the complexity and mysteries surrounding Phantom Limb Pain which will be discussed later, however it is clear than any pain phenomenon experienced post amputation has links with Phantom Limb Pain.

4.2.2 Back Pain following amputation

An overlooked aspect of pain post amputation, but one aspect which is common is back pain [30]. Lower limb amputees [77] who found back pain more bothersome than Phantom Limb Pain [78] and also upper limb amputees. A 2009 study on chronic pain within a selected upper limb amputee population by Hanley et al [79] reported that 52% amputees suffered back pain and 43% experienced neck pain.

Back pain isn't the only concern for upper-limb loss since the procedure increases the risk of self-reported musculoskeletal pain in the shoulders, and in the remaining arm [80] along with potentially bad upper limb posture. [81][82][83].

4.2.3 Phantom Limb Phenomenon, Awareness and Sensation

Phantom Limb phenomenon was first described and studied by Mitchell in 1871 [84]. The phenomenon is described as "the sensation that an amputated or missing limb (even an organ, like the appendix) is still attached to the body and is moving appropriately with other body parts."[85]. With a more contemporary explanation from Hunter et al as "sensory experience that is perceived to originate from the missing body part"[86]. This phenomenon therefore is the general definition that encompasses the feeling and sensation of missing a limb. Along with Phantom Limb Phenomenon two other sub conditions exist, Awareness and Sensation.

Phantom Limb Sensation refer to somatic sensory experiences experienced by the amputee

both exteroceptive and/or proprioceptive sensations in nature. Such sensations as the missing limb feeling tinglingly, itchy, applied pressure on the limb, random movement and the sensation of the missing limb feeling hot or cold. The percentage of the amputee population who would describe their Phantom Limb Sensations as above according to Hunter et al in 2003 is around 13-24% [87] however Jackson et al [64] report that "Its (Phantom Limb Sensation) incidence is very high, with virtually all amputees describing phantom limb sensations".

This sensation is non painful [88] and includes the feeling of the limb telescoping [64] in that the missing limb has the sensation of moving towards the stump or away from the stump. Research by Wilkins et al in 1998 [89] with 60 congenital amputees suggests that those who are born without a limb experience significantly less phantom sensations than those due to surgical means.

Post amputation of a limb or other body part leads to a feeling that the limb or body part is no longer there (Phantom Limb Awareness) defined as a general awareness that the limb is missing rather than a specific somatic sensation [87].

This sensation does not provide much concern for the amputee, although a significant percentage of amputees (47-71%) [86] with Koojiman in 2000 reporting up to 80% [82] feel their phantom as a general awareness that they experience the presence of the missing limb rather than specific somatic sensations [90].

This is considered separate to Phantom Sensations which unlike the sense of awareness is more specific to sensory and kinaesthetic sensations felt by the amputee. Such sensations are the position and orientation of the missing limb, telescoping or shortening along with additional sensations. This non painful sensation of the phantom limb present is experienced by both congenital amputees and those who have had an amputation via traumatic or non traumatic means [90]. Although this sensation part of the Phantom Limb Phenomenon is experienced regardless of cause of amputation as highlighted by Flor and colleagues in 2006, the pain part of the phenomenon is experienced mainly by adults, and is rarely present in children and extreme cases in congenital amputees [91].

4.2.4 Phantom Limb Pain

4.2.4.1 Definition and Characteristics

Pain as a result of Phantom Limb phenomenon (also called phantom limb pain) has been reported to be present in 50-80% of amputees with implications to the quality of life of those experiencing the symptoms [57]. A recent systematic review [92] suggests that the prevalence of Phantom Limb Pain from 1980 to 2019 is around 64%. Limakatso and colleagues have also suggested that the prevalence of Phantom Limb Pain was significantly lower in developing countries compared to developed countries [53.98% vs 66.55%; p = 0.03]. Although as discussed in chapter 2 with civilian casualties in war-zones, this data might not be a true reflection of the geographical prevalence. Pain can have a negative effect on rehabilitation outcome due to varied range of symptoms (e.g. wetness/burning/locking sensations).

Due to the nature of pain and the complexities that arise due to the amputation, characterisation of Phantom Limb Pain is often personalised to the individual.

However Figure 4.1 demonstrates some of the more common pain sensations that both lower and upper limb amputees experience. It should be added from participant discussions that multiple types of these pain types can exist. The figure also neglects more temperature based pain types such as freezing or burning sensations which can result in higher levels of pain.

These types of pain discussed above are clearly extremely distressful and cause chronic (primarily located in distal parts of the missing limb[94]) and acute pain [95] with pain spikes or breakthrough pain [96] which can occur in situations such as stress or for no apparent reason at all .

4.2.4.2 Previous Research on Phantom Limb Pain

The previous two main theories attempting to explain phantom limb pain can be categorised into peripheral nervous system and central nervous system mechanism based approaches. However more recent and generally more accepted notion is that cortical reorganisation is responsible for Phantom Limb Pain as mentioned in the work of Weeks and colleagues [97]. This recent work has been backed up by studies carried out by [98] and [99]. Although these studies suggest possible mechanisms relating to phantom limb pain, the work carried

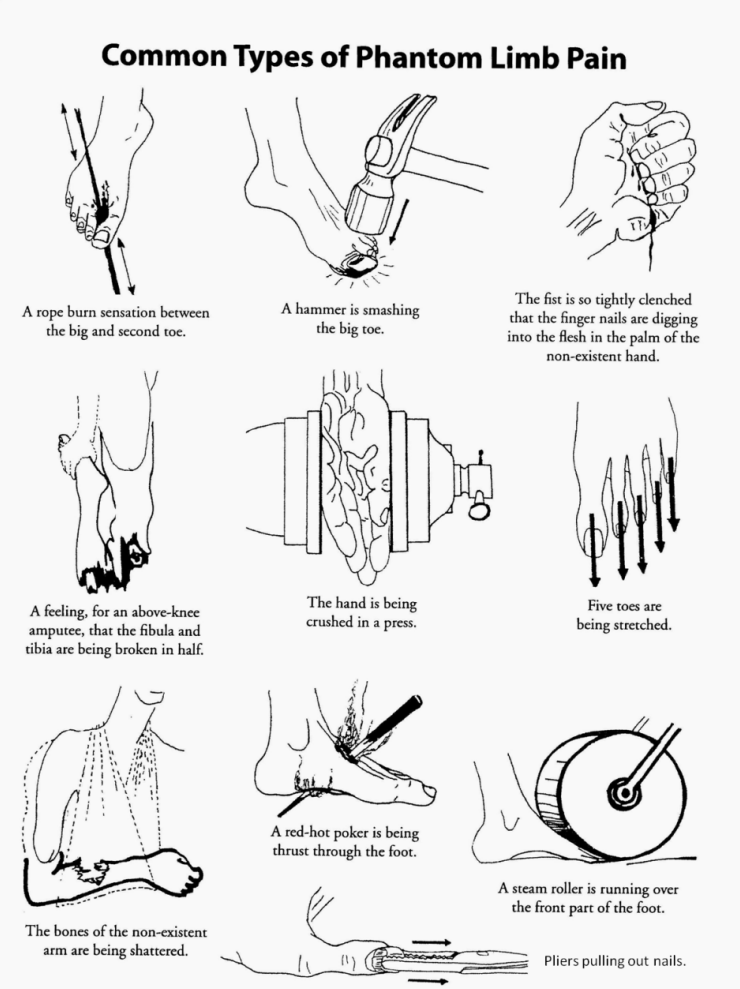


Figure 4.1: Most common types of pain symptoms of upper and lower limb Phantom Limb Pain. Diagram extracted from [93]

out by Tsao and colleagues [100] have postulated the concept of proprioceptive memory. This theory is based on the view that the brain keeps possession of a memory of specific limb positions and that post amputation this results in a conflict amongst the brain and visual system. This concept compliments previous work that focuses on the visual system's role and the effect this has on cortical reorganisation related to pain reduction [101][102][103]. The result of which is that a correctly position limb is presented to the participant were their missing limb should be correcting the specific limb position. Previously three factors were put forward to attempt to explain the various areas which contribute to Phantom Limb Pain; Peripheral, Spinal Plasticity and Cerebral Reorganisation which the following sections cover those details as discussed in Nikolajsen et al's work [104].

Peripheral factors

Phantom Limb Pain has been shown to be more frequent and significantly more painful

with amputees who experience long-term stump pain [105][106]. Previous work has suggested that Phantom Limb Pain decreases with less stump disease or injury post amputation [105], although the majority of the work carried out supporting these claims are based on early research from the 1970's and onwards, these have been reported with a total cohort of 60 participants. However these early studies do provide a comprehensive look at Phantom Limb Pain in general providing detailed separation between Phantom sensation, Phantom Limb Pain and Stump pain. Although these early studies lack neuro imagining techniques they do attempt to provide a solid foundation to try to explain potential peripheral factors could contribute to Phantom Limb Pain.

Spinal plasticity

Spinal plasticity and factors could be considered the next link in the chain when looking at factors associated with Phantom Limb Pain. Research involving local anaesthesia administrated to the stump, plexus or spine are not effective at eliminating Phantom Limb Pain, leading to ongoing work pointing in the direction of more central/spinal factors. Birbaumer and colleagues conducted a study with a small cohort of amputees suffering from Phantom Limb Pain [107]. 50% of the participants (3 out of 6) experienced near elimination of their pain within 20 mins of the anaesthesia being administrated with the other 50% having no pain relief with a nerve block located in the brachial plexus. In addition to pain scales, MRI scans were used to examine the cortical changes potentially taking place, with Birbaumer and colleagues observing sudden cortical reorganisation in the somatosensory cortex within the 50% of participants who experienced pain relief yet no cortical reorganisation with the participants who did not experience any pain relief. However Birbaumer and colleagues suggest that this relationship of cortical reorganisation and phantom limb pain with regards to their findings might have a causal relationship, due to low numbers of participants.

This has lead research by Schmidt et al [108] in 2005 to focus on the spinal pathways and its relationship to Phantom Limb Pain by inducing Phantom Limb Pain via spinal anaesthesia. This is based on previous work on lower limb amputees who suffer from Phantom Limb Pain carried out originally by Mackenzie in 1983, based on inducing severe lightning pain in the lower limbs [109]. Although both research studies are lacking in numbers of participants and rigorous studies, they do highlight the spinal factor in the formation and maintaining of

Phantom Limb Pain. The lack of observed spinal changes in terms of neurons and cortical pathways within this research does call into question the exact mechanisms and the role the spinal factors play however, after nerve injury there has been shown to be an increase within the general excitability in just not spinal cord neurons but associated C-fibres leading to secondary pain signalling neurons. This is more commonly known as central sensitisation [110] within dorsal horn neurons is started by the production of glutamate and neurokinins resulting in mechanical hyperalgesia and an expansion of peripheral receptive fields [111].

Cerebral Reorganisation

The phantom limb concept, by its definition is complex in its nature, with both a range of inputs and outputs that can effect the phantom. From the site of injury to cortical areas various parts play a role in its construction. Researchers have suggested that this phantom may be a construct from the brain.

Electrophysiological studies have documented the existence of nociceptive specific neurons and wide dynamic range neurons in the cerebral cortex. This was shown following limb amputation and deafferentation of adult monkeys, where there is a reorganisation of the primary somtosensory cortex, subcortex and thalamus [112].

After dorsal rhizotomy, a lowered threshold required to evoke activity in thalamus and cortex can be demonstrated. Also, adult monkeys display cortical reorganization in which the mouth and chin invade cortices corresponding to the representation of the arm and digits which have lost their normal afferent input [113].

In humans, similar reorganisation has been observed using magnetoencephalographic techniques. Interestingly, this cerebral reorganisation was seen mostly in patients with phantom pain and there was a linear relationship between pain and degree of reorganisation [114]. Changes have also been observed at more subcortical levels. Using neuronal recording and stimulation techniques, Davis and colleagues found an unusually large thalamic stump representation [115].

In 1989 Melzack published his review on Phantom Limb Pain and put forward a hypothesis for the pain as a neuromatrix [116]. This was based on previous work looking at individual case studies of patients who underwent surgical transection of the spinal cord. This in addition to receiving a sympathetic block prior to the surgery yet experienced painful

phantoms afterwards which seemed unplauseable at the time since the current understanding at the time was that link between the periphery and the brain via the spinal cord was severed and thus pain could not be transmitted. Melzack postulated that explanations for such phantoms and the pain resulting in painful phantoms must involve the brain. He further questioned the identification of Phantom Limb Phenomena within the post-central somatosensory cortex explaining that "Excisions of the somatosensory cortex for Phantom Limb Pain, show that with elapsed time both the phantom limb and pain both return" [116].

Melzack then put forward his neuromatrix idea, arguing that previous work involving body schema within a phantom limb content is weak due to nerve blocks. Inputs from millions of nerve impulses terminate in the brain from various systems and sub systems of the body (cutaneous/proprioceptive/visual/vestibular) which as a whole make up the experience of the body. As a result Melzack's neuromatrix theory in essence described a "genetically built-in matrix of neurons for the whole body (which) produces characteristic nerve-impulse patterns for the body and the myriad somatosensory qualities we feel" [116]. The hypothesis is backed up from Melzack's and other colleagues observations on paraplegics with high-level complete spinal breaks and despite the lack of inputs from some parts of their bodies various sensations both good and bad can be experienced. Even with hyperactivity in spinal cells above the level of the break these sensations can still be felt. It is the "anatomical substratum of the physical self" Melzack writes that is comprised of a network of neurons spread across the brain that yields these continued sensations post injury. Genetically these neurons and synapses might have been distributed however can be modified as a result of sensory inputs. A digram of this model can be seen in Figure 4.2 with the body-self matrix being comprised of sensory, affective, and cognitive neuromodules.

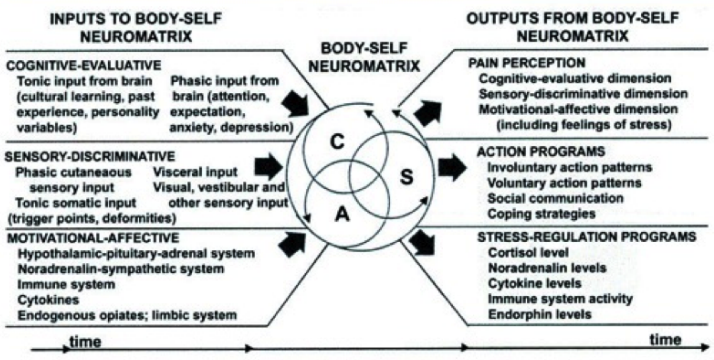


Figure 4.2: Melzack's Neromatrix in diagram form, showing both inputs and outputs that change the body self matrix. Extracted from [117]

Melzack's model gained traction the model filling missing or at the time incorrect aspects suggested in previous studies. Also due to the models behaviour based on Hebbian learning, removing the top down approach found in previous models and promoting competition synaptically in his model which either promoted or retract synaptic connections, which in turn would lead to a more natural model of pain.

Melzack's model is also important since it combines not just pain but body awareness, which is missing from previous models, highlighting that many systems and subsystems place a role in providing input to the brain in terms of processing pain. Of particular interest is the model's stressing of sensory based input. It is these inputs, cutaneous in particular that has been the basis for subsequent theories on Phantom Limb Pain discussed in the next section. Criticisms of Melzack's model stem from it's simplistic nature and lack of validation when applied to a range of patients along with post amputation effects on the nervous system and the changes these have on Phantom Limb Phenomena. It does act again as a catalyst to changing the approach to modelling pain emphasising biological ideas in such a basic model. This basic model has provided groundwork for testing hypothesis for nearly 30 years of research not just for Phantom Limb Pain but other pain conditions.

4.2.4.3 Current Trends in Research on Phantom Limb Pain

Behavioural therapies stemming from research suggested that Phantom Limb Pain could be the result of plastic changes within the sensorimotor nervous system. Flor and colleagues in 1995 first demonstrated a strong link between the amount of cortical reorganisation and the magnitude of Phantom Limb Pain [118] within a population of upper limb amputee sufferers. This very early work using MRI data does highlight a shift within the cortical map post amputation highlighting the neurophysiological aspects of Phantom Limb Pain rather than previous research which assumed the opposite of this Flor's research but still supporting Melzack's Neuromatrix model. Studies since 2004 have been developed in an attempt to normalise the representation of the phantom hand. These therapies involved mirror box/visual surrogate/graded motor imagery paradigms in order to help the amputee move the phantom limb/hand. The reason why these behavioural therapies focus on increasing phantom limb/hand movements is due to the increased research showing this type of therapy could lead to Phantom Limb Pain levels to decrease. However methodical evidence linking

the part this phantom limb/hand motor control has in predicting or regulating Phantom Limb Pain still eludes researchers.

The more recent work using state of the art neuro imaging has lead to a drastic re-examination of the relationship between Phantom Limb Pain and brain organisation.

Recent research on Phantom Limb Pain has focused on cortical representations and the connections between cortical areas primarily involved in hand areas, with some research also looking at the missing arm area too.

Reilly et al in 2008 published work disputing previous research suggesting that the amputated hand area "disappears" suggesting that in fact it does not disappear. In addition the team proposed putting forward a "two levels of hand-movement representation" model within the primary motor cortex pre and post amputation [119] one level specifying limb movements purely as hand and arm motor commands and the second level specifying limb movements purely as muscle maps (Figure 4.3), addressing missing elements and adding to Melzack's neuromatrix model. The paper concludes that cortical reorganisation within the primary motor cortex post amputation effects mainly the upper limb's muscles but not its associated motor command map. It is this motor command map and its durability that plays a role in the existence of the phantom limb, hypothesising that post amputation "the hand representation sends the hand motor commands to the remaining muscles via preserved descending outputs, which are then perceived by the patient as phantom limb movements"[119]

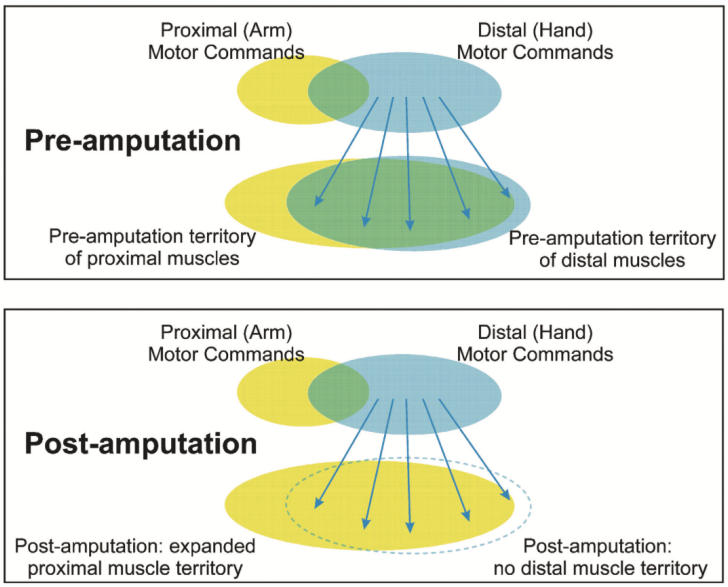


Figure 4.3: Reilly et al's two level motor cortex movement organisation pre/post amputation. Diagram extracted from [119]

Describing Figure 4.3 based on previous studies carried out by the authors and others suggests that two separate levels of hand movement representation could potentially exist together in the primary motor cortex.

Reilly et al postulated that cortical reorganisation within the primary motor cortex post amputation focuses mainly on the muscle map instead of the motor command map used for the hands and arms. Therefore any occupation as a result of amputation in other cortical areas would take place at the muscular level thus preserving any remaining motor commands responsible for hand movements intact. This would give rise to Phantom Limb movements of the missing hand experienced by amputees which persist despite being cut off from the hand and arm muscular map. There is a possibility of hand motor commands being directed from subsequent areas in the premotor areas as opposed to the primary motor cortex.

Using this two level model yields a global limb and muscle implementation level which could be used to suggest why post amputation phantom hand movements persist and can be seen in the activation of the amputee's motor cortex, also fitting in with the general consensus of post amputation cortical reorganisation.

In 2013 Makin et al published their work suggesting that chronic phantom pain experience drives plasticity by maintaining local cortical representations and disrupting inter-regional connectivity rather than the fore mentioned maladaptive cortical reorganisation, triggered by loss of sensory input [120].

Makin et al suggests that "phantom pain experiences are decoupled from other sensorimotor experiences, the lack of co- activation of the cortical phantom area and other body parts (such as the intact hand) may result in diminished interactions between different body part representations." [120]. Makin et al used MRI data of amputees suffering from Phantom Limb Pain within brain areas representing the missing hand in order to come to this conclusion, rather than the representations of the neighbouring non amputated body parts previously focused on by MRI studies.

They concluded that with "while loss of sensory input is generally characterised by structural and functional degeneration in the deprived sensorimotor cortex, the experience of persistent pain is associated with preserved structure and functional organisation in the former hand area. Furthermore, consistent with the isolated nature of phantom experience,

phantom pain is associated with reduced inter-regional functional connectivity in the primary sensorimotor cortex" [120] proposing that "contrary to the maladaptive model, cortical plasticity associated with phantom pain is driven by powerful and long-lasting subjective sensory experience, such as triggered by nociceptive or top down inputs" [120].

Kikkert et al [121] used MRI scans to quantify cortical changes of those suffering chronic Phantom Limb Pain by requiring 14 upper limb amputees to voluntarily move their phantom limbs in a finger tapping test; with those amputees suffering higher levels of Phantom Limb Pain having less control of their phantom fingers due to poor motor control. Kikkert and colleagues suggested via MRI scans that there could be a relationship between slower phantom hand movements and a stronger activity in the primary sensorimotor phantom hand cortex (complementing Reilly et al's work), which had in prior research been demonstrated to be associated with chronic Phantom Limb Pain. This work highlights the importance of phantom hand movements and the link between the quality of movements in terms of motor skills and also pain levels. It also demonstrates that potentially improving phantom hand movements could possibly lead to a decrease in perceived levels of pain, however this link is casual in nature and requires further investigation, increasing the importance of attempting to position and engage the phantom limb and hand as correct as possible in any future therapies. It is important to note that although previous visual surrogate therapies exist (covered in subsequent chapters) they heavily focus on motor imagery but neglect any aspect on motor execution of the phantom limb highlighting why these therapies are considered to be ineffective in reducing perceived levels of pain. Therefore any movement based therapies should focus on attempting to improve actual movements of the phantom hand using growing research as the basis for this claim. Interestingly the concept that motor command or the lack there of applies to more than just phantom hand movements. Raffin et al [122] similar to Kikkert's work in using MRI, Observed cortical reorganisation within the hand area of the brain, with no changes in the areas representing the lip and elbow. They observed that poorer motor skills measured similar to Makin's work within the fingers of the phantom hand resulted in higher levels of perceived pain which also lead to these changes in the lip and elbow cortical areas. This again strengthens the plasticity model of Phantom Limb Pain and also suggests that the motor skills of the Phantom Limb share a direct relationship with cortical reorganisation post

amputation but also that these changes previously thought to be purely related to the face and hand now extend to the upper limb as a whole and medial part of the sensorimotor cortex.

Kikkert and colleagues replicated their work again in 2018 to stress the link between chronic phantom limb pain and maintained missing hand representation[123], again suggesting that those amputee participants suffering from higher levels of chronic Phantom Limb Pain experience stronger activity in the primary sensorimotor cortex of their missing hand whilst performing movements with their phantom hand during the study. However unlike their previous work in 2016 no lip remapping occurred to the missing hand areas thus suggesting that "the correlation between chronic Phantom Limb Pain and maintained representation of the missing hand cannot be explained by the experience of chronic non-painful phantom sensations or compensatory usage of the residual arm or an artificial arm (prosthesis)" and that "Together, our results reaffirm a likely relationship between persistent peripheral inputs pertaining to the missing hand representation and chronic Phantom Limb Pain, and emphasise a need to further study the role of peripheral inputs from the residual nerves to better understand the mechanisms underlying chronic Phantom Limb Pain."[123]. This recent work strengthens and extends Melzack's model in that many systems and sub system play a part but also highlight the difficulties in pin pointing any exact cause of Phantom Limb Pain. However still highlighting peripheral inputs from the residual limb and nerves.

Research published in 2021 by Erlenwein, Diers and colleagues[124] provides a state of the art overview regarding Phantom Limb Pain including its mechanisms and existing theories, stating that "Therapy focusing on limb perception (such as mirror therapy and prosthesis use) could prevent, reduce, and even reverse these changes in cortical reorganization". Makin's research has put forward theories such as the disruption of interregional functional connectivity rather than by changes in the local cortical representation, which also includes preserved structural representation of the area of the amputated hand. Makin's work does suggest that the theories previously on maladaptive reorganisation might not be true, however as Erlenwein and colleagues have suggested via work carried out by Boström and colleagues, in which a computational model was developed to test the existing theories of Phantom Limb Pain[125], that both "the amount of reorganization during tactile stimulation (used by Flor et al) and the level of cortical activity during phantom movements (used by Makin

et al) were enhanced in a scenario with strong phantom pain as compared to a scenario with weak phantom pain. Thus, depending on the experimental context or method chosen, one might find evidence for either cortical reorganization or preservation of the amputated limb representation. Both cortical reorganization and preservation might not be contradictory, but rather complementary, which should be considered in future PLP models."[124].

It is this, the combination of tactile simulation and movement of the amputated limb which is used as a base for the core concepts of the system created as part of the PhD. The element of a purely visual approach clearly has some effect on pain but it is the combination of tactile feedback along with movement of the amputated limb in a virtual space which is core to the system constructed. These concepts are discussed in the next two chapters looking at treatments for Phantom Limb Pain.

4.3 Summary

This chapter has provided an overview of the different pain phenomena experienced post amputation in addition to describing the previous and current theories on the mechanisms of Phantom Limb Pain.

What makes Phantom Limb Pain hard to describe and also to lay a foundation in which to start developing therapies in treating is the complexities involved in its mechanisms. Advancements in neurological scanning technology has provided insights which enable researchers in neuroscience to focus on particular areas as opposed to previous work.

During the timeline of the PhD the theories behind Phantom Limb Pain have evolved rapidly, with the idea of Melzack's neuromatrix model and others being dominate during the start of the process. These lead to more neuro imaging based research being published mid way through the PhD, with conflicting yet complimentary theories being published at the end of the PhD.

A recent essay by Makin[126] in 2021 briefly summarised current theories behind Phantom Limb Pain. Highlighting issues with mirror box type of paradigms. However as Makin states arguing that a purely visual system "cannot trick somatosensory cortex into reorganising with visual information, simply because visual input is not a powerful modulator of this particular brain area". This quote compliments the paradigm developed

as part of the PhD, as the main addition to the system is that of haptics, the sense of touch. On the other hand it is argued that the combination of movement of the amputated limb and haptics has merits in terms of cortical reorganisation and preservation of the missing limb. As such one could argue the inclusion of haptics described in this thesis has always been inspired by this notation that purely visual based approaches would not be enough to have any cortical effect. This is further backed by recent work carried out by Erlenwein and colleagues[124] that there is no set definition of the mechanisms and those that do exist do so not in a vacuum but compliment each other.

The next chapter reviews treatments for Phantom Limb Pain as well as expanding the visual and tactile elements discussed in the previous section with regards to its implementation in potential treatment for Phantom Limb Pain.

Chapter 5

Treatments After Amputation for Phantom Limb Pain

5.1 Introduction

Over the years a vast range of treatments have been proposed in order to treat Phantom Limb Pain. However as eluded to in the previous chapters the complexity and difficultly in understanding Phantom Limb Pain has lead to slow progress in treatments. Giummarra and Moseley in 2011 [127] provided a relatively robust overview and updates of treatment options from a traditional sense however this chapter will extend the discussion of treatment options to include modern technological based approaches.

5.2 Traditional

In 2002 Flor and colleagues [128] summarised the research on Phantom Limb Pain and treatment. These treatments were also updated in review papers published in 2011 [127] and 2021 [124]. The five categories listed in the following sub-sections by Flor will be used to provide an overview of traditional Phantom Limb Pain treatments supplemented by Giummarra and Moseley et al updating the sections when necessary. Although important to note Flor et al does stress the lack of effectiveness of traditional treatments stating that "A maximum benefit of about 30% has been reported from treatments such as local anaesthesia, sympathectomy, dorsal-root entry-zone lesions, cordotomy and rhizotomy, neurostimulation methods, or pharmacological interventions such as anticonvulsants, barbiturates, antidepressants, neuroleptics, and muscle relaxants." [128]. This statement straight away highlights the problems with selected traditional treatments. Hampered by the fact "Most studies have been uncontrolled short-term assessments of small samples of patients" [128]. Giummarra et al also strengthens this view stating that "Many treatments to

date have shown little benefit in pain reduction, particularly pharmacological treatments and invasive treatments involving surgery." and that "Physical, psychological and behavioural treatments that replace or substitute the absent afferent signals from the amputated limb show the greatest promise for reducing phantom pain." [127]. This statement does support the thesis work combining physical, psychological and behavioural treatments, thus moving away from invasive treatments such as surgical interventions unless absolutely needed.

5.2.1 Surgical

Surgical intervention traditionally involves either stump revision or neurectomy as a result of complications post initial amputation, but can also include [128]:

- Stump revision
- Neurectomy
- Sympathectomy
- Rhizotomy
- Cordotomy
- Tractotomy
- Dorsal column stimulation
- Deep brain stimulation

More recently Targeted Muscle Reinnervation (TMR) surgery has been initially used to improve more intuitive control of a prosthetic device [129]. The process involves "excision of the sensory neuroma, followed by coaptation of the proximal ends of the transected sensory nerves to the cut motor nerves of nearby non-functional, dennervated muscle targets"[130]. The process is considered a "well-studied, low-risk, and successful procedure"[129] in which pain reductions outcomes are now being studied as a possible treatment for post amputation pain. Although the surgery is more common in the US it is not currently offered on the National Health Service (NHS) in the UK. This is due to the surgery first needing to be shown as consistently more effective than current treatments along with the NICE advocating the use of non-invasive pharmacological therapy as first-line management of neuropathic pain [130]. In addition the cost of TMR needs to be examined compared to existing non surgical treatments, however as Bawa states "It is likely that acute TMR performed at the

time of amputation would prove to be globally cost-effective as it may prevent the formation of neuroma-associated pain in the first place."[130]. However in the UK there are around 5200 upper limb amputations a year[131] requiring potentially thousands of TMR surgical procedures in addition to those who have already had their amputation and are suffering from post amputation pain, who due to circumstances might not want further surgery. As more clinical studies look at TMR as a pain treatment option in combination with cost effectiveness, in the future TMR could potentially be used in more cases within the UK.

Stump revision requires further surgical intervention post initial amputation. Reasons for performing stump revisions include:

- Stump pain and/or phantom limb pain.
- Late infection of the stump.
- Symptomatic bone spurs.
- Revision of a skin graft used primarily to conserve stump length.
- Improvement of the stump for prosthetic fitting.

Stump revision is often needed and can effect the outcome of rehabilitation and quality of life with Liu et al in 2015 showing that significant improvements in ADL scores were shown pre and post admission with lower limb amputees after stump revision [132]. Stump scarring out of 80 stump revisions according to Lie et al accounted for the majority of revisision (52.5% [132]). An example of lower limb stump scarring and associated revision can be seen in Figure 5.1.

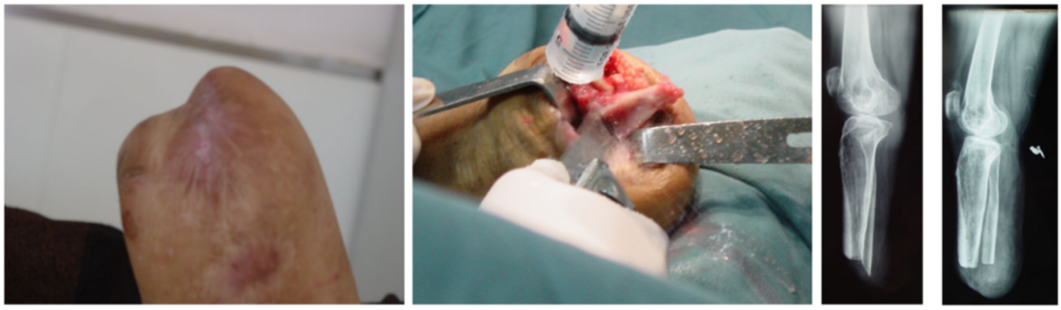


Figure 5.1: Example of a lower limb stump which required a stump revision with clear scarring and associated stump pain influence weight-bearing. Extracted from Liu et al [132]

Woods et al [133] in 1987 examined how effective the value of revision surgery when carried out more than six weeks after initial amputation of the upper or lower limb. Of 284 patients were surveyed only 11% of whom suffered from stump/phantom pain achieved

"satisfactory results" after one revision procedure. In addition 73 patients required further revisions post initial procedure.

Therein lies the issue of performing a stump revision in order to treat Phantom Limb Pain which the intervention is both complex and expensive which could lead to additional post operational rehabilitation. Similar to TMR surgery more clinical studies as well as efficacy studies would need to be carried out to examine if surgical interventions perform better than non surgical interventions discussed below.

5.2.2 Pharmacological

Pharmacological intervention along side psychological based interventions are most commonly used to help treat Phantom Limb Pain with various degrees of success and effectiveness.

Previous work carried out by Nikolajsen and colleagues [134] has suggested preamputation pain is associated with increased Phantom Limb Pain within a population of 56 lower limb amputees, with 42% of the patients reporting that their Phantom Limb Pain resembled the preamputation pain. Although this study looked at lower limb amputees which could provide different results for upper limb amputees it does present the issue of relieving pain prior to amputation. The use of pre-emptive analgesia is seen to be an effective measure to decrease postoperative pain [135][136] however this is not the case for Phantom Limb Pain as highlighted by Ypsilantis et al review on the topic in 2010 suggesting "There is no robust evidence supporting the use of pre-emptive analgesia to minimize the risk of chronic pain after amputation" [137].

A 2009 study by Roullet et al examined "the influence of preoperative opioid consumption on postoperative morphine consumption after leg amputation performed under combined regional and general anesthesia." [138]. Roullet and colleagues suggest that "Despite the use of regional anesthesia, chronic opioid consumption before leg amputation is associated with increased postoperative morphine consumption and phantom limb pain"[138].

This further raises questions preamputation, with pharmacological intervention being included in treatment options post amputation. Due to the many areas related to Phantom Limb Pain pharmacological intervention can include drugs such as [128]:

- Conventional analgesics

- Opioids
- β - blockers
- Neuroleptics
- Anticonvulsants
- NMDA-receptor antagonists
- Ketamine
- Memantine
- Antidepressants
- Barbiturates
- Muscle relaxants

Of the above list the most commonly prescribed are "tricyclic antidepressants, anticonvulsants and opioids" [127]. Of these Pregabalin and Gabapentin are the most common, used to treat epilepsy and neuropathic pain with both having similar common side effects such as headaches, feeling sleepy, dizziness, memory problems, mood changes, swollen arms and legs, blurred vision and dry mouth [**?**][139]. Long term use of this medication does involve whether the user can tolerate the common short term side effects [140]. Pregabalin and Gabapentin causes multiple side effects some of which can cause permanent damage even after relatively short periods of use [141] which does question their use in treating Phantom Limb Pain.

In terms of overall effectiveness of pharmacological intervention a systematic review by Finnerup in 2010 concluded that "A large proportion of neuropathic pain patients are left with insufficient pain relief. This fact calls for other treatment options to target chronic neuropathic pain." [142]. As Subedi et al, backed by Weeks et al suggests "Opioids provide analgesia without the loss of touch, proprioception, or consciousness. They may also diminish cortical reorganisation and disrupt one of the proposed mechanisms of Phantom Limb Pain." [143][97]. For these reasons, the continued use and prescription of this type of intervention could be seen as beneficial despite side effects[144].

5.2.3 Anaesthetic

Anaesthetic intervention treatments as seen below are short term treatments. The most common prescribed being nerve blocks, used to block pain from a nerve, whose admin-

istration is guided by an X ray or CT. In terms of efficacy, Flor describes as "(anaesthetic blocks) do not uniformly eliminate phantom-limb pain or they eliminate it for a period that clearly exceeds the time the block can be active." [128]. The duration the block can be active normally between 18 to 24 hours [145] depending on the chemical compound of the block, however this can be shorter or longer with some blocks lasting weeks and some lasting less than a few hours. Due to this current studies on the efficacy and evidence are lacking related to blocks used post amputation [146].

Other commonly used anaesthetics during or just after the amputation are listed below[147].

- Epidural blockade
- Sympathetic block
- Local anaesthesia
- Lidocaine

In terms of efficacy between the blocks a 2019 review concluded that "Of the currently available studies comparing the other approaches, there seems to be little difference in efficacy between axillary, supraclavicular and infraclavicular approaches for elbow, forearm and hand surgery when equivalent levels of expertise are used"[148].

5.2.4 Psychological

It is clear from the above that non invasive methods of treatment are required that attempt to provide effective pain relief without short or long term side effects. The list below gives an exhaustive overview of such treatments as stated by [127][128]:

- Electromyographic biofeedback
- Temperature biofeedback
- Cognitive-behavioural pain management
- Sensory discrimination training
- Hypnosis
- Transcutaneous nerve stimulation (TENS)
- Acupuncture
- Physiotherapy

- Ultrasound
- Manipulation
- Prosthesis training/use
- Mirror Box Therapy

Of this exhaustive list the main focus will be on prosthesis training and mirror box therapy due to the close relation to the thesis work.

Prosthesis use has been shown to reduce phantom pain due to embodiment [149][150][151]. Flor and colleagues in 2021[152] examined the relationship between prosthesis ownership and Phantom Limb Pain within a population of 2383 amputees utilising questionnaires. Their study suggests that those with higher levels of prosthesis ownership experience lower levels of Phantom Limb Pain. However, the association of prosthesis ownership was observed to be independent of the frequency of use. It is believed that the amputee's perception rather than the pure use of the prosthesis is associated with phantom limb pain. This is opposed to previous work suggesting that simply using a prosthesis is associated with lower levels of Phantom Limb Pain. In a recent report focusing on the use of physical prostheses [153], Page and colleagues suggest that ownership (another form of embodiment) depends on plausible anatomical orientation (of the prosthesis) along with temporal and spatial synchrony of both visual and tactile feedback. This is discussed in greater detail in chapter 6 examining embodiment and Phantom Limb Pain.

Learned non-use could be defined as "a learning phenomenon whereby movement is suppressed initially due to adverse reactions and failure of any activity attempted with the affected limb, which then results in the suppression of behaviour. Continuation of this response results in persisting tendency and consequently, the individual never learns that the limb may have become potentially useful. As such, therapies such as constraint-induced movement therapy (CIMT) explored below have been developed to combat learned non-use. There seems to be a strong link between phantom limb pain and limb non-use and it is postulated that these two related effects have an impact on cortical reorganisation. The importance of supervised practice on the other hand, or exercises using impaired upper limbs in order to combat limb non-use and to lessen the effects of such conditions has been high-lighted by work carried out by Taub et al [154]. Supervised practice as shown by Taub

has lead to an increase of motor skills. Although Taub's study focused on stroke patients, it has been acknowledged that this also applies to other brain injuries as well. Experimental work on monkeys with a single forelimb surgically abolished sensation [155] showed that the animals choose not to use the deafferented limb despite having enough motor innervation to do so. Interestingly, this apparent dissociation is also present in humans following neurological trauma. Taub's studies demonstrate the benefits of methods found in Constraint-Induced Movement therapy (CI therapy) in helping lessen the effects of learned nonuse.

5.2.5 Mirror Box Therapy

Visual illusions therapies such as mirror box therapy (shown in Figure 5.2) which was first developed by Ramachandran and colleagues in the early 1990's [101] as a potential treatment to Phantom Limb Pain. Their suggestion was that the use of a mirror could potentially reverse the cortical reorganisational changes observed in those suffering from Phantom Limb Pain. In order to test this nine upper limb amputees participated in an experiment in which a large mirror was placed in front of them in such a way so that the participants could see the mirror reflection of their normal hand "superimposed" on the phantom hand. Participants were instructed to perform mirror symmetric movements whilst looking at the mirrored image on the amputated side. Once the normal hand moved the phantom was visually perceived to move allowing a vivid kinaesthetic sensation to emerge. The participants used the mirror box over a three week period everyday for fifteen minutes, with a number of participants experiencing different effects such as telescoping of the phantom limb, reduced spasms of the hand and reduced pain[156][157].

Figure 5.2: An example of the mirror box being used by an amputee. Extracted from Ramachandran et al [7]

Multiple theories have been suggested to explain how visual feedback has an effect on perceived levels of pain such as maladaptive cortical reorganisation put forward by Flor, Diers[102] and Murray[103] who has looked at using Magnetic Resonance Imaging (MRI) whilst using mirror visual feedback. Manipulation of sensory and motor integration within the central nervous system was put forward by Ramachandran and others like McCabe[158] based on the comparator mechanism discussed in chapter 4. Lastly, that mirror visual feedback could relieve pain by creating a sense of ownership, based on the rubber hand illusion, visually embodying the mirrored image of the intact limb resulting in reduced sensory input and pain. Embodiment is discussed in the next chapter in detail.

A review of clinical studies involving evaluating mirror box therapy for treating Phantom Limb Pain was published by Wittkopf and Johnson in 2021[9]. The review examines eight randomised control trial studies totalling 1619 participants from 2011 until 2021, conducing that evidence for the efficacy of mirror visual feedback is inconclusive (due to the stratified population). However the therapy does reduce pain in subgroups of patients when used as a course of treatment [9]. With issues such as a lack of standardised protocols for clinical use of mirror box therapy, however suggesting that the studies reviewed highlight home use of the therapy. Embodiment of the mirrored image located where the missing limb is being viewed, along with synchronisation between movement and perception is important in reducing pain. Standardising the therapy using technology including virtual reality has been suggested in improving the outcomes of mirror box therapy. This is due to tailored patient specific

representation of their phantom limb synchronised with movement of the amputated limb.

One issue that the physical mirror box raises as shown in Figure 5.2 is the narrow view in order for the therapy to have an effect. This requires the patient to remain in a fairly fixed position and to ignore the limb providing the movement. These issues can be addressed with virtual reality as discussed in the next section. However due to the low cost and lack of side effects mirror box therapy has become an attractive option at attempting to treat Phantom Limb Pain.

What mirror box therapy paradigms do provide is visual movement of the amputated limb as per chapter 4's discussion on current trends in Phantom Limb Pain research. Using a physical mirror box provides basic movements visually using the intact limb, however using technology such as virtual reality allows movement and tracking of the amputated limb and also due to immersive virtual reality can mask any lack of limb movements so that movements are scaled up. In addition, the use of haptics which allows tactile sensation also ties into current research presented in chapter 4 discussed below and in the next chapter.

5.3 Technology Based

An increase in visual quality and decrease in costs of virtual reality headsets has lead to the investigation of virtual reality mirror box therapy, to address the issues of narrow view and immersing the patient. First looked at in 2005 by Kuttuva et al [**?**] based on mirror box therapy, this field of work has now been extended into the domain of Augmented Reality and other vision based technology such as Kinect.

5.3.1 Virtual Reality

Virtual Reality is generally thought of a computer graphic scenario or environment that simulates a realistic experience. Virtual reality systems have been used in many domains such as robotics, video games, entertainment, training and healthcare therapies.

As stated previously the use of the phrase "virtual reality" when describing a system does not require it to use a head mounted display. This is evident in many virtual reality and some augmented reality systems which will be discussed later on. However one element which has not been discussed is that of user input.

Traditional and current virtual reality systems would use a keyboard and mouse to

facilitate user input or in the case of specialist simulations such as Figure 5.3 use custom input to a virtual system, allowing unlimited input devices into a system.

Figure 5.3: Example of a specialist virtual reality simulation involving custom user input, in this case a parachute harness allowing user movement to appear accurately virtually

Recently more innovative solutions involving visual tracking and detection and more sensor based approaches such as the 3gears system, as shown in Figures 5.4 and 5.5 utilising camera based input, with sensor based examples such as the myo shown in figure 5.6 and the Oculus Touch controllers in Figure 5.7.

Figure 5.4: 3gear natural vision based hand tracking set up and example useage

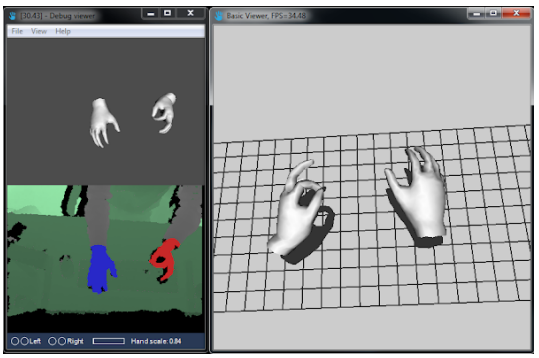


Figure 5.5: Screenshot showing the 3gear system tracking the left and right hand correctly and displaying the separate hands graphically

Figure 5.6: Myo, with integrated EMG sensors and gyroscope to detect arm position

Figure 5.7: Oculus Touch controllers. For use alongside the Oculus Rift head mounted display which tracks the position and orientation of each hand as well as any button input

The introduction of inexpensive and mass produced 3D vision systems such as the Microsoft Kinect has enabled researchers and developers to produce algorithms to take raw feeds such as depth streams combined with visual streams to track whole hands and detect gestures such as the 3gears system.

The major drawback to the input systems mentioned above in relation to constructing and using a virtual reality system for an amputee is that full use of one or both arms and hands are needed. Therefore input systems which do not focus on tracking hands need to be used. Systems such as the Myo as seen in Figure 5.6 or custom made devices and software allow positioning and orientation of a limb not just a hand in virtual space. The Myo is an armband which uses bluetooth to communicate the position and orientation of the upper arm and any muscle activity thanks to the EMG sensors surrounding the inside of the armband and proprietary EMG classification. However one major drawback to the Myo is the armband has to be located just above the elbow meaning that for transhumeral amputees the system could not be used.

In terms of systems designed around all levels of upper limb amputees, it is therefore mandatory to construct custom solutions to allow user input beyond EMG control in order to facilitate position and orientation movement of a virtual limb and also opening and closing of the virtual limb via EMG.

Initial work using virtual reality with amputees relied either on simple EMG control to allow a visual representation of a hand open and close to be displayed on a computer screen along with very simple movements derived from custom input devices such as Kuttuva

et al's device [**?**] shown in Figure 5.8 using FSR sensors.

Figure 5.8: A transradial amputee participant using the system developed by Kuttuva. Extracted from [**?**]. Input to the virtual system is taken from EMG sensors to facilitate grasp and release with basic movement of the residual limb taken from FSR sensors.

In Kuttuva's pilot system which focused on a single transradial amputee did not look at phantom limb pain, but did examining the possibilities in using EMG and FSR sensors on the stump in order to manipulate a virtual hand to accomplish simple tasks.

Subsequent research such as Murray's 2006 work [8] directly translated traditional mirror box therapy into a virtual reality domain solving the issue of a fixed head position. The study involved 5 upper limb amputees suffering from Phantom Limb Pain. Participants were tasked with performing simple exercises using their intact limb which was mapped to their amputated side virtually using a data glove. Various pain questionnaires such as the full McGill questionnaire (taken at the beginning and very end of the follow up session) and short McGill pain questionnaire (taken at the end of each session) were taken along with the participants completing a pain diary. Five participants (3 upper limb, 2 lower limb) took part in the study over 2.5 months. One negative aspect in Murray's work is that due to the study duration not all of the participants completed the 10 sessions but all participants completed at least 7 sessions lasting 30 minutes each. Another negative aspect is that Murray does not present the short McGill pain questionnaire values as part of the results section instead focusing on the qualitative pain diary and feedback. Overall Murray sums up the study in terms of pain as "all participants did make reference to a decrease in experienced phantom limb pain whilst immersed in the virtual environment. This is a positive result which should be investigated further." [8] subsequently no other studies have been published by Murray or

his group. It should also be added that no control group was present for this study, but does suggest that such an approach can be used for Phantom Limb Pain treatment by building on previous work carried out using mirror therapy. However what is missing from Murray's study is the quantitive pain results and a more robust longer term study.

Figure 5.9: A transhumeral amputee participant using the system developed by Murray et al. Extracted from [8]. Input to the virtual system is taken from the data glove located on the intact hand mapped to the opposite amputated limb.

Following Murray's initial work in 2007 Hauschild et al [159] created a head mounted display virtual reality system looking at training amputees to use advanced upper limb myoelectric prosthetic devices in a virtual environment performing simple object manipulation.

In 2008 Al-Jumaily et al [160] created a virtual reality system using EMG to train amputees to move a virtual arm and hand in 10 separate classes of movement. The 10 classes of movement were:

- Forearm Pronation/Supination
- Wrist Flexion/Extension
- Hand Ball Grab/Release
- Hand Open/Rest
- Wrist Radial/Ulnar Deviation

Similar to the work carried out by Kuttuva, Al-Jumaily's work in 2008 does not focus on pain but using virtual reality as a rehabilitational training tool, although in this case no ADL exercises were performed and the initial paper focused on validation of the system.

The theme running through these initial studies in virtual reality does appear to look at rehabilitional training, in potentially training amputees to use via EMG a myoelectric prosthesis rather than pain. One reason this could be the push for myoelectric prosthesis from 2006 onwards coinciding with DARPA launching the "Revolutionizing Prosthetics" program which aimed to speed up development of advanced artificial upper limb prosthetics. Another aspect of these earlier systems is the use of software to create the virtual reality

environments. Specific engines such as Unity and Unreal Engine were either not widely used in public due to licensing or hadn't been developed yet. All of these early systems used a combination of software such as Java3D, Matlab and Simulink to visualise the graphics.

It wouldn't be until 2010 when Bach et al [161] published concept work on using immersive virtual reality via a 3D head mounted display as a phantom limb pain therapy using the mirror box therapy paradigm. Building on the work by Murray in 2006, the system utilised augmented reality to detect opening and closing of a hand in an fMRI scanner.

The use of virtual reality and robotics applied to Phantom Limb Pain therapy within a upper limb population is rare, however in 2011 Lambrecht et al [162] published concept work on using virtual reality, EMG and use of a robotic interface as a myoelectric prostheses training tool and testing of new myoelectric prostheses.

More recently systems have been developed as part of research projects such as the VITA - Virtual Therapy Arm project from DLR [163] which like previous research is aimed at training the user to use a myoelectric prostheses as seen in Figure 5.10. The VITA project ran from 2016 to 2017 and although did not look at the phantom limb pain therapy benefits of such a system did manage to recruit a transradial amputee to help test the system.

Figure 5.10: A amputee using the VITA system which uses the myo in order to achieve input to the system. Extracted from [163].

Utilising the Unity game engine the VITA system graphically is very impressive with the HTC Vive allowing the user to walk around a virtual environment. The use of the myo armband provides high quality EMG pattern recognition with hardly any set up, which allows simple opening and closing of a virtual hand. But this does limit the type of amputees who could use such a system for example transhumeral amputees or those with poor muscle signal strength in their lower arms. One more serious negative point about the VITA which

could have large implications for prospective Phantom Limb Pain sufferers is highlighted in Figure 5.10. A common occurrence in immersive virtual reality is the issue of floating hands. Work by Martini and colleagues [164] have suggested that perceived colocation of the real and artificial limb (physical or virtual) might be necessary for the analgesic ownership effect to take place. Implementing anatomically correct inverse kinematics from an end effector is not an easy task given the limitations of the users (in this case amputees) or for the general population. For an amputee to see a realistic hand floating where their amputated hand should be could be seen as jarring and unnatural.

In 2016 work by Ortiz-Catalan et al [165] reported on the results of an augmented/virtual reality system (Figure 5.11) for use in Phantom Limb Pain therapy with a cohort of 14 upper limb amputee participants. Participants used the system for 12 sessions lasting 2 hours each with follow up sessions at 1, 3 and 6 months being conducted after the last sessions to examine any long lasting changes in pain. An augmented reality marker was placed on the anterior of the amputated stump to visually retrieve the position and orientation of the stump with EMG sensors being placed on the stump to facilitate grasp and release.

Figure 5.11: Augmented Reality system by Ortiz-Catalan et al showing the set up of the system and a participant from the corresponding study using the "immersive" exercises. Extracted from [165]

.

The outcomes in terms of pain reduction were reported to be 47% (SD 39) from pre session to last treatment session, weighted pain distribution for the numeric rating scale 32% (SD 38) and 51% (SD 33) for the pain rating index. These results will be discussed further in comparison to the work carried out for this thesis due to the similarity of the clinical trail

set up. However the work carried out by Ortiz-Catalan et al does not include a control group.

The work carried out by Ortiz-Catalan does distinguish itself from work such as Murray in that the web camera set up tracks the affected limb as opposed to Murray's studies which uses cameras or tracking gloves on the intact limb in order to provide input to the system, which as Ortiz-Catalan suggests "makes these solutions methodologically equivalent to mirror therapy" [165] with the benefit of tracking the affected limb providing the location (co-location) of the virtual limb. What is missing from these tracking systems which is implemented in Ortiz-Catalan's work in the opening and closing of the phantom hand which is achieved via EMG.

Shortcomings of Ortiz-Catalan's work include not taking any measurements on embodiment or agency which is highlighted in the paper. However the paper does stress the inclusion of tactile feedback as most approaches use visual only feedback to which other sensory feedback (tactile) need to be evualated in terms of contribution towards Phantom Limb Pain relief. The system presented in the thesis addresses this in terms of sensory feedback and a initial feasibility clinical study to examine the effect of tactile feedback.

Looking back on the technological based treatments, there is a distinct grouping of work, with the majority focused on non-pain therapy. This as eluded to above could be due to the push of advanced myoelectric prosthesis from 2006 onwards. Recent advancements in technology have enabled researchers to create truly immersive virtual reality systems and decoupling the mirror box paradigm (e.g using the amputation limb to make movements as opposed to the intact limb in physical mirror box therapy) to allow the amputated limb to function as much as it can do virtually, aided by head mounted display units and sensor and vision based technology.

It should be added that there is much variation in what constitutes a virtual reality experience. It is clear that those systems with a head mounted display in 3D with tracking capabilities are far more immersive than those systems who do not use such equipment. The use of robotics in combination is also one area that is rarely used, perhaps due to the cost of some robotic equipment,

Table 5.1 provides an overview of the existing work carried out with amputees using technology either for prothesis training or Phantom Limb Pain treatment. Those studies

which did not include participants are indicated as N/A in the final column.

Modern technology interventions Overview				
Name	Year	VR/AR	PLP or Prosthesis training	Number of participants
Kuttuva et al [**?**]	2005	VR	Prosthesis training	1
Murray et al [8]	2006	VR (Immersive)	PLP	5
Hauschild et al [159]	2007	VR (Immersive)	Prosthesis training	N/A
Al-Jumaily et al [160]	2008	VR	Prosthesis training	N/A
Bach et al [161]	2010	VR & AR	PLP	N/A
Lambrecht et al [162]	2011	VR & Robotics	Prosthesis training	N/A
VITA [163]	2016	VR (Immersive)	Prosthesis training	1
Ortiz-Catalan et al [165]	2016	VR/AR	PLP	14

Table 5.1: Table showing overview of existing technological interventions

Of those highlighted in the table, only 3 have focused on Phantom Limb Treatment paradigms, with 2 of these having cohorts of amputees who suffer from Phantom Limb Pain. Difficulties in recruiting participants due to time constraints, number of participants and development of technology perhaps has lead to relatively few studies looking at implementing modern technological elements to help with Phantom Limb Pain.

Therefore the following aspects should be included in subsequent research to fill in the missing gaps proposed by previous research:

- The use of immersive virtual reality, in order to compensate the limitations of physical mirror box therapy and allow decoupled exercises.
- In order to increase said immersion fully anatomically correct inverse kinematics for both the amputated limb and intact limb, based on the kinematics on the intact limb and using position/orientation data from sensors for the affected limb. In the case of the paradigm created for the study, the end effector data.
- In addition to the previous point, use of a fully rendered avatar to aid in immersion by reducing any negative side effects that Phantom Limb Pain suffers might experience if incorrect postures etc are present, as discussed by Martini and colleagues [166] and also expanded in chapter 6. This could eliminate the "floating hand" problem faced by many immersive virtual reality systems currently available, strengthening research by Page and colleagues.
- Provide biofeedback to increase the level of agency and functional embodiment that

the participant experiences. For example using EMG to open and close the virtual hand using muscles from the amputated limb.

- Provide force feedback to also further increase levels of functional embodiment and agency. Discussed in the next chapter when describing the rubber hand illusion.
- Provide both quantitive and qualitative measures of pain over the course of any clinical study. The McGill pain questionnaire is clinically validated and also allows both quantitive and qualitative measures of pain.
- Ensure both short and long term intervention with regular follow up sessions in order to assess the effect the intervention the system has on perceived pain levels.
- A control group must be present, this is lacking in all known virtual reality Phantom Limb Pain technological therapies.

5.4 Summary

In this chapter both traditional and modern technological interventions and treatments have been looked at. It is clear that due to the complex nature of Phantom Limb Pain and the lack of background understanding that effective treatments still elude the medical community. This is most clear from a review in 2002 by Halbert et al [167] which looked at Phantom Limb Pain pain management studies from 1966-1999 using various methods of intervention. Halbert et al concluded that there was insufficient evidence to support the efficacy of any of them (treatments) stating "Although up to 70% of patients have phantom limb pain after amputation, there is little evidence from randomized trials to guide clinicians with treatment. Evidence on preemptive epidurals, early regional nerve blocks, and mechanical vibratory stimulation provides inconsistent support for these treatments. There is currently a gap between research and practice in the area of phantom limb pain." However it is clear that moving away from a pharmacological approach provides benefits in terms of cost both short and long term and towards the health of the sufferer due to side effects of common drugs prescribed. Previous studies on Phantom Limb Pain management suffer from many issues as highlighted by Richardson et al [168] in 2017 over 38 studies with a range of treatments such as small sample size and inactive placebo, concluding with "Robust studies on homogeneous populations, an understanding of what amputees consider a meaningful reduction in PLP

and agreement of whether pain intensity is the legitimate therapeutic target are urgently required." [168]. Due to the nature of amputation it is hard to conduct a study with a homogeneous population, and something which the study in this thesis couldn't achieve. The main technological issues the virtual reality only systems mentioned in the chapter is the lack of tactile feedback, which the paradigm produced for the feasibility clinical study includes.

Chapter 6

The relationship of Phantom Limb Pain between Embodiment and Agency

6.1 Introduction

The previous chapter looked at potential treatments for Phantom Limb Pain, where it was highlighted that most treatments focused on only the visual representation of anatomically correct limbs. The provision of haptic feedback beyond imaginary movements of the residual limb has not been explored and might provide a different treatment alternative. Recent publications[124][153] highlights the importance of evaluating the contribution of other forms of sensory feedback beyond visual in terms of phantom limb pain relief. Motor control coupled with visual and tactile feedback is discussed in this chapter and forms the basis for the designed system that will be described in chapter 7.

The core concept presented in this chapter is that of visually embodying the representation of the "intact" limb where the missing/ residual limb is located, coupled with agency, which is the self belief that one is making the movements that are visually embodying. This chapter thus examines two concepts: 1) how embodiment and agency applies to Phantom Limb Pain, and 2) how to extend and enhance these concepts to maximise treatment effectiveness.

6.2 Embodiment

6.2.1 What it means

Embodiment has been described as "the sense of one's own body" [169] and is a well known phenomena in psychology also called "coenaesthesia", "bodily self-consciousness" and "corporeal awareness". Both visual and multisensory cues can lead to embodiment [170][171], involving the extrastriate body area (EBA) in the lateral occipitotemporal cortex (which processes images of bodies, body parts real and imagined and executed movements)

and the temporoparietal junction (TPJ) in the cortex which integrates multisensory body related information. However much has been debated over the years about its meaning and importance. Important to the context of this thesis, is the concepts regarding embodiment and subdivision of body representation mainly body image and body schema which stem from embodiment. This phenomenologically complex nature of embodiment is used primarily for self recognition [172] in that the feeling of being distinct from other objects and persons is one component of the sense of embodiment [173]. Being distinct from objects and other people provides your perspective of the world around you internally. This internal bodily experience can be perceived as binding your own experiences within the borders of your physical limits [174]. This internal bounding when applied to pain serves to localise where pain occurs, e.g when hammering a nail and hitting a thumb the pain is felt in the thumb and hand area rather than the foot [174].

Embodiment is mainly used for self recognition, a concept suggested by Povinelli [175] using the idea of a mirror to recognise one's self. Povienelli suggested that "to learn to recognise oneself in a mirror requires one to recognise the equivalence between the movement of the image and the movement of one's body" [175]. Povienelli follows this by providing a method of self recognition using a mirror; "One must recognise that what is true of one's body is also true of one's mirror image. This is done by comparing movement of one's body to that of the mirror image. For this to work, the subject must recognise that the body and the movement in question have something to do with them. In other words the subject must recognise that the body that moves is one's own, that it is the body one is bounded in, and the movements that they control that are reflected in the mirror. That is, mirror self recognition requires, in part, the sense of embodiment." [175]. This quote directly follows into the sense of agency, in that "one must possess a sense that one initiates, controls and ends the actions one performs" [175]. The concept therefore of self recognition is deeply linked between the visual and self regulated control of one's movement.

Embodiment has also been referred to as the sense of ownership[176] and has even extended into research [177] to show that non-amputees over a short time can feel the sense of embodiment of a telescoped amputated limb. Research has been conducted on embodiment, with the rubber hand illusion (RHI) being a popular test of the sense of embodiment (as

shown in figure 6.1. Also called the sense of ownership (SOO for short [176]).

In order for the rubber hand illusion to work, participants sit at a table with their forearms resting on a the table and either their left or right hand hidden inside a box or a divider to which they can not see their forearm and hand. A lifelike rubber hand is then placed in front of the participant either on the left or right side (which is hidden) and lined up with their left or right shoulder to visually seem anatomically correct. A cloth covered the stump of the hidden hand, but the fingers remained visible for the participant to see. The experimenter strokes the middle finger of the participant's real hand using a fine brush, while simultaneously stroking the same finger on the rubber hand at the same time and speed for up to two minutes. This helps combine the visual aspect that the participant sees their hand being touched with the tactile feeling of being touched. At a random time the experimenter produces a hammer or mallet and hits the rubber hand, producing the reaction that the participant has had his or her hand hit despite it being the rubber hand that is being hit.

Figure 6.1: Example of the Rubber Hand Illusion, showing the set up of both the covered actual hand and the rubber hand visible to the participant. Extracted from Moguillansky et al [178]

The main benefit in using the rubber hand illusion to showcase how embodiment works aided by tactile touch is hightlighted by Tsakiris et al [179] supported initially by Botvinick and Cohen in that "the rubber hand illusion (RHI) reflected a three-way interaction between

vision, touch, and proprioception: Vision captured touch, resulting in a mislocalization of the tactile percept toward the spatial location of the visual percept. This visual-tactile correlation influenced the felt position of one's own hand." [179]. It is the synchronisation of both the visual and tactile inputs that allow embodiment of the rubber hand. Vision usually plays a dominant role over touch and proprioception, although the use of touch and proprioception is more used for fine movements and adjusting movements. These concepts of providing tactile input to the rubber hand reinforce the ideas of providing a binding of embodiment in that the participant believes his or her hand is being stroked. Due to the simplicity the rubber hand illusion has been ported into a virtual domain with research conducted by IJsselsteijn et al in 2006 [180], Yuan et al [181] in 2010 and Slater et al [182] in 2009 to name but a few.

Regardless of whether the rubber hand illusion is performed in a real or virtual environment it does provides a framework that shows the importance of multisensory integration. But also the relationship between vision, touch, and proprioception it provides researchers a quantitive measure of the level of embodiment discussed in the section 6.2.2. When examining the effects of a surrogate limb virtually on the amputee population is an important area to study in both combining visual and tactile feedback to enhance embodiment. Both visual and multisensory cues can lead to embodiment [170][171]. Lotze and colleagues have suggested that the use of a prosthesis has been shown to lower the perceived levels of phantom limb pain within sufferers [151].

6.2.2 How embodiment is measured

Due to the complex nature of embodiment measuring it is challenging. The main method suggested by Botvinick and Cohen in 1998 [183] using the rubber hand illusion to measure the level of embodiment derives from a series of questions to gauge the participant's level of embodiment of the rubber hand asked after the intervention which consisted on a single session. The questionnaire states nine questions about the level of embodiment. Due to the open nature of the questionnaire subsequent studies have implemented variations of the original set of questions put forward by Botvinick [183][184][185]. These include modifying the questions to ask about a virtual hand as opposed to a rubber hand.

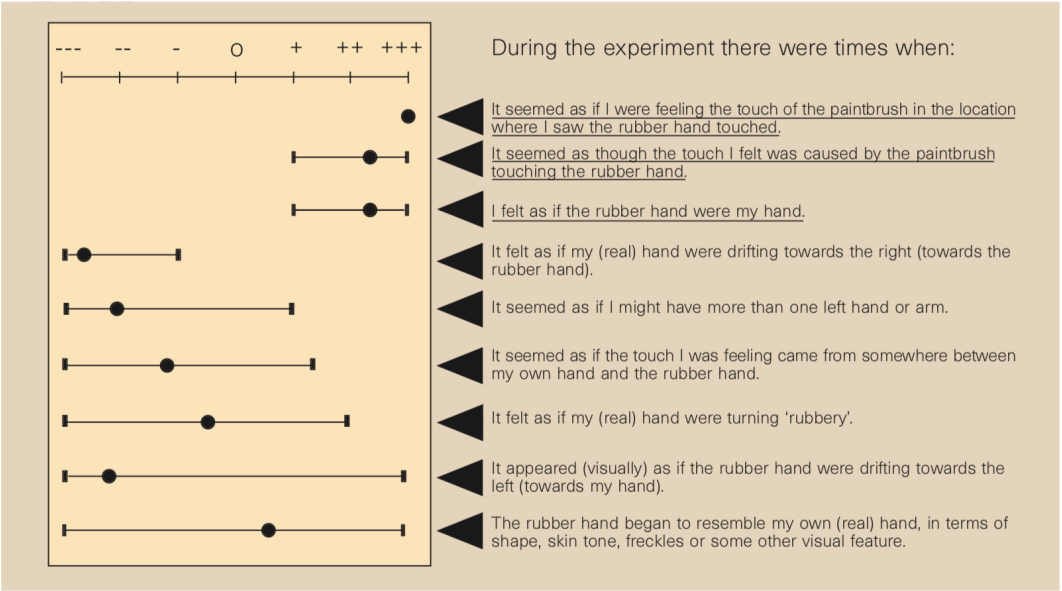


Figure 6.2: The original results of the embodiment questionnaire showing the results and questions. Extracted from Botvinick et al [183]

The benefit of using such a questionnaire is that the questions can be tailored to the specific experiment, be it based in the real or virtual domain. These questions can also be broken down into sub-groups based on general embodiment and embodiment control. However some of the questions can seem vague when a control group is used, such as when no tactile stimulation is used.

Quantitative measures such as proprioceptive drift estimation (as shown in Figure 6.3) have been used by numerous studies [185][186][180] to gauge the distance participants believes their limb has moved during the session. This measure is taken pre and post experimental session to measure the effectiveness the visual and tactile input has had on the level of embodiment towards either a rubber or virtual hand. The results are traditionally measured in the x axis (transverse plane, going left to right of a participant) only from the tip of the middle finger in order to locate the middle of the hand in x axis terms and is reported in centimeters.

Unlike the embodiment questionnaire, the execution of the proprioceptive drift measurement is quick and understandable to the participant and is less likely to produce incorrect results due to human error. This has been suggested by Page and colleagues[153] as a more reliable and repeatable measure of embodiment.

More recently studies combined with virtual reality such as Spanlang et al [188] in 2014 have used electroencephalography (EEG) alongside physiological measurements such as galvanic skin response (GSR) etc to measure levels of embodiment. However the standard

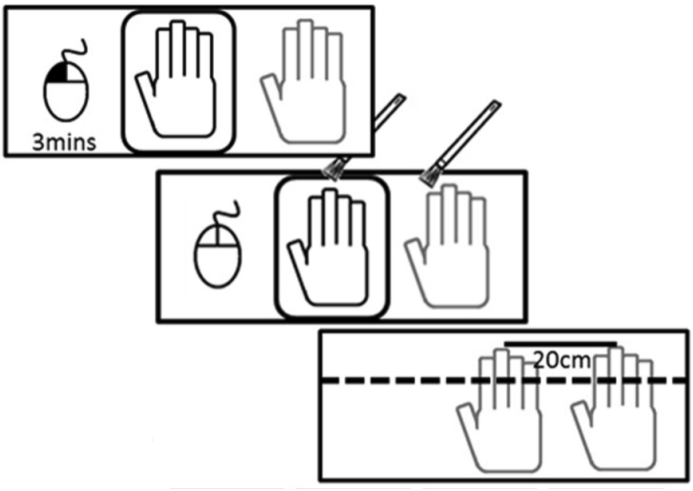


Figure 6.3: An example of proprioceptive drift measurement taken during a rubber hand illusion experiment showing the measurements in the x axis of where the participant thought their hand was and where it actually is. Extracted from Wold et al [187]

methods of measuring embodiment is still dominated by questionnaires and proprioceptive drift measurement, but with advancements in brain imagery this could well change.

It should be noted that measurement mentioned above (questionnaires and proprioceptive drift), are used mainly in short term studies lasting minutes rather than hours. This is due to these measures being applied to single session experiments such as the rubber hand illusion or variants of the experiment. This does pose the question of the long term variability of using such methods, Page and colleagues [153] suggest as mentioned before the perceived phantom hand location as a suitable embodiment metric.

6.3 Sense of Agency

6.3.1 Overview

As briefly mentioned above, the sense of agency although related to embodiment is quite distinct. A 2008 review of the the sense of agency including an overview of experiments by David et al describes the sense of agency as "the sense that I am the one who is causing or generating an action. For example, the sense that I am the one who is causing something to move, or that I am the one who is generating a certain thought in my stream of consciousness" [189]. This distinction differentiates the sense of agency over the sense of embodiment/ownership in that embodiment provides the sense that you are undergoing an action or movement whether or not that movement is voluntary or involuntary. However

the differences can be blurred. An example of this is passive arm movements highlighted by Tsakiris et al [190] in that both agency and embodiment both occur and participants find it difficult to tell each sense apart. Tsakiris and colleagues suggest that multisensory signals interact with body representations to first generate the sense of embodiment, with the sense of agency modulating the sense of embodiment [190]. Tsakiris and colleagues also suggest that efferent and afferent signals linked to the central nervous system are crucial for both embodiment and agency, with afferent signals providing agency and efferent signals supporting embodiment. Generally these models are used to describe both motor control and optimisation, action awareness using this model has also been examined [191][192]. Combining action awareness to the forward model yields the sense of agency using an efference copy of an action and therefore predicting subsequent sensory actions. If the predicted and actual outcome of this action is true then the sense of agency arises, whilst if the predicted and actual outcome of the action is false then this can been seen as another agent and as a result not invoking the sense of agency as shown in the schematic in Figure 6.4.

The system produced for the thesis uses this model as the participants visually see an intact representation of their missing limb, but they are controlling the movement of this limb. Once the participant starts moving their affected limb in space and sees an intact representation moving correctly this attempts to correct sensory outcomes both visually and via motor commands. This then corrects the predicted and actual outcomes and increases levels of agency.

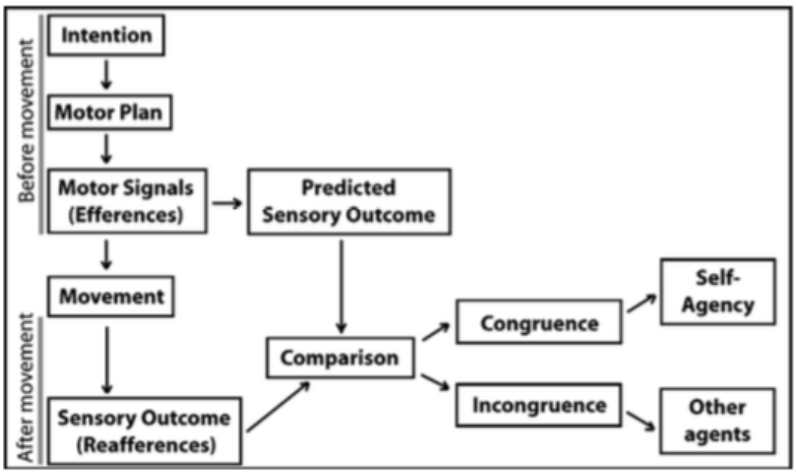


Figure 6.4: Schematic of the central monitoring theory otherwise known at the comparator model. Extracted from [189]

6.3.2 How it is measured

Similar to the sense of embodiment, the sense of agency is somewhat difficult to reliably measure. As a result questionnaires such as the ones mentioned in the embodiment section are modified to include questions on the sense of agency, a recent example being from Marasco et al [193] in 2018 as seen in Table 6.1. However in 2008 Farrer et al [194] investigated the use of MRI scanners to pinpoint the cortical areas involved in the sense of agency. Farrer and colleagues suggest that the right inferior parietal area, most notably the right angular gyrus are heavily involved with the sense of agency using a delayed visual feedback technique to distinguish between the cortical areas. This suggests that this cortical area is involved in "higher-order aspects of motor control that allows one to consciously access different aspects of one's own actions. Specifically, this region processes discrepancies between intended action and movement consequences in such a way that these will be consciously detected by the subject. This joint processing is at the core of the various experiences one uses to interpret an action." [194].

6.4 How Embodiment and Agency relates to Phantom Limb Pain

As discussed in the previous chapter one treatment option to amputees who suffer from Phantom Limb Pain is that of mirror therapy. As mentioned above embodiment is mainly used for self recognition. Previous work from Foell et al using mirror box therapy, where an intact limb has been shown to decrease pain in Phantom Limb Pain sufferers [195] as a result of visually correcting the representational restitution of the missing limb in the brain. Effects were predicted by a telescopic distortion of the phantom, with functional magnetic resonance imaging measurements suggesting a relationship between pain and cortical reorganisation pre and post mirror therapy.

This is also suggested previously by prosthesis use in which a study in 1999 showed a decrease in perceived levels of Phantom Limb Pain [196]. However subsequent studies by Lotze et al [197] have called this early link into question using MRI scans to look at cortical reorganisation levels. However visually, prostheses ownership might have an effect on self recognition and embodiment. The visual and physical properties of the prosthesis also might

have an effect of embodying the prosthesis. A range of upper limb prothesis is shown in (Figure 6.5), one potential reason why prosthesis use might not be as effective in aiding self recognition is due to the colour and physical configuration (hand or hook) of the prosthesis.

Work by Aymerich-Franch et al in 2017 has shown that non-human looking robot arms can induce embodiment within a healthy population cohort of 31 participants [199]. Additionally Aymerich-Franch et al demonstrated that embodiment towards the non-human looking robot arm is also perceived when visuo-movement synchronisation is used instead of visuo-tactile stimulation [199] again highlighting the importance of the sense of agency and its role in embodiment.

More recently in 2017 Makin et al [200] showed that prosthetic limbs when used to substi-

Type	Statement
Embodiment	I felt as if I was looking at my own hand.
	I felt as if the virtual hand was part of my body.
	It seemed as if I were sensing the movement of my fingers in the location where the virtual fingers moved.
	I felt as if the virtual hand was my hand.
Embodiment control	My residual limb began to feel rubbery.
	It felt as if I had three hands.
	It was almost as if I could see the virtual hand moving towards my residual limb.
	The virtual hand started to change shape, color, and appearance so that it started to (visually) resemble the residual limb.
Agency	The virtual hand moved just like I wanted it to, as if it was obeying my will.
	I felt as if I was controlling the movements of the virtual hand.
	I felt as if I was causing the movement I saw.
	Whenever I moved my hand I expected the virtual hand to move in the same way.
Agency control	I felt as if the virtual hand was controlling my will.
	I felt as if the virtual hand was controlling my movements.
	I could sense the movement from somewhere between my residual limb and the virtual hand.
	It seemed as if the virtual hand had a will of its own.

Table 6.1: Example of both an embodiment and agency questionnaire. Extracted from Marasco et al [193]

Figure 6.5: Small selection of upper limb prosthesis and hand attachment. Extracted from [198]. The range of shapes, colours and mechanisms which could lead to users not embodying them.

tute the missing hand, can recruit brain resources normally devoted for body representation, with a direct link between embodying artificial limbs which depends on the individual's prosthesis usage in everyday life. Individuals who rely more on their prosthesis to substitute hand function show stronger activity in hand-selective visual areas. The research also shows "that prosthesis usage also shapes large-scale brain reorganisation, specifically intrinsic connectivity between visual and sensorimotor hand-selective areas" [200], again highlighting the link of not just the visual aspect of embodiment but the sensorimotor aspect of agency.

Work by Flor and colleagues published in 2021 [152] have further suggested links with embodiment and ownership related to lower levels of Phantom Limb Pain. One outcome of their recent study suggests that both prosthesis ownership and frequency in use of the prosthesis lead to less severe post amputation pain "Univariate correlations revealed that both prosthesis ownership and the frequency of prosthesis use were significantly negatively associated with the severity of postamputation phenomena"[152].

These results are of correlative nature, due to a causal relationship. Flor and colleagues also state that the experimental induction of ownership in terms of the rubber limb illusion or related paradigms can reduce acute pain perception although there are contrary findings to this. The association of prosthesis ownership was independent of frequency of use, it was the amputee's perception of the prosthesis rather than purely the frequency of use which is associated with less post amputation pain. Perception in regards to perceived colocation of

the real and artificial limb (either prosthetic or virtual) as Martini [166] suggests is necessary for the ownership effect to take place. Page and colleagues[153] also strengthen this view that embodiment depends on "plausible anatomical orientation, temporal and spatial synchrony (between the visual and tactile feedback)". Flor and colleagues concluded that overall sensory feedback both "enhances ownership and reduces Phantom Limb Pain"[152].

Interestingly as highlighted by David et al [189] despite a large number of experiments (1963-2007) involving the sense of agency; 14 were carried out as behavioural studies within a healthy participant cohort, 11 were carried out as behavioural studies within schizophrenia patients, 16 were simple activity experiments based on neuroimaging measures with a healthy cohort, and 2 neuroimaging studies similar to the healthy population but with schizophrenia patients, making 43 in total, and despite the list not being exhaustive there is a lack of either upper limb or lower limb amputee studies.

This is surprising since the majority of studies which involve a Phantom Limb Pain cohort focus on the sense of embodiment and not on agency, despite agency being a subcomponent of embodiment[201]. This also partly relates to criticism of mirror box therapy as put forward but Makin[126] as a result of visual only. In addition research discussed below by Page et al [153] suggesting motor control of the affected limb as a way of increasing embodiment. Perhaps this is due to the equipment available to researchers, the issues of moving an amputee's arm without robotic intervention and immersive virtual reality does cause problems physically. This is addressed in the system produced which can facilitate the amputated limb being attached to the robot and moving the arm 1 to 1 virtually and the participant having control opening and closing their missing hand via EMG electrodes.

This is also supported by Flor and colleagues in 2021[152] who's work examined the relationship of prosthesis ownership and Phantom Limb Pain after surveying 2383 amputees. Their work based on a 53 item questionnaire modified from the Phantom and Stump Phenomena Interview suggests a number of findings:

- The younger the amputee the more the prosthesis owner felt ownership over the prosthetic device.
- In addition, the longer the residual limb on the affected side reflected more ownership of a prosthetic device.

- Amputees who wore prosthetic devices with greater levels of functionality rather than cosmetic non functional devices also experienced greater levels of ownership.
- As a result of the analysis the authours suggest it is not just ownership of a prosthetic device that participants stated reduced pain but also the frequency of use of said device.
- However the association of prosthesis ownership was independent of the frequency of use but also the users perception of the device rather than the mere use of a device that is attributed to lower pain levels.

The work is a prospective study which is addressed in the paper however the conclusion is that "there is some evidence that more naturalistic prosthetic devices equipped with sensory feedback both enhance prosthesis ownership experiences and reduce PLP levels. Identification of the underlying mechanisms of the relationship of pain, prosthesis use, and body perception could facilitate the development of better prosthetic devices that potentially reduce postamputation pain."[152]. Again highlighting the importance of sensory feedback in terms of embodiment.

The idea of the prosthesis being "part of them" highlighted by Carruthers et al and colleagues [202] due to the body schema being up to date does stress that controlling the prosthesis leads to deeper levels of embodiment as opposed to visually due to the sense of manipulation and tactile feedback. This is also suggested by Page and colleagues[153] who examined motor control and sensory feedback as a method of enhancing embodiment and its effect of reducing Phantom Limb Pain. Page and colleagues suggest that visual fixation produces the smallest amount of embodiment as opposed to motor control and sensory feedback.

6.5 Summary

Despite the similarities between the two concepts of embodiment and agency, there is much debate within research regarding sense of embodiment or agency having an impact on the amputee and ownership of a limb [203][204][205]. Previous research has stressed this focus, however the mirrored image is that of the intact arm resulting in the sense of agency that could perhaps be called into question. The suggested architecture and physical make up of the clinical feasability study outlined in chapter 8, does lend itself more to allowing upper limb amputees to carry out movements and actions with their amputated limb more

so than previous work in an immersive environment. Although embodiment still plays an important role it is clear that complimenting embodiment with agency is an element the research should focus on due to the inclusion of voluntary movement which could have an impact on Phantom Limb Pain, as highlighted by Page and colleagues[153]. Although mirror box therapy does contribute to pain reduction as discussed in the next chapter despite effectiveness issues, the addition of engaging the sense of agency could be the missing part which might improve visual based treatment methods.

As discussed in the previous chapter research has utilised technological approaches to attempt to provide pain relief. However the main feature that the previous research has not addressed is the element of enhancing embodiment via tactile feedback. This is partly due to the lack of proper immersive VR systems which have been created for Phantom Limb Pain treatment but also a lack of tactile/force feedback in such systems. It is this combination of immersive VR and force feedback in terms of haptics that the system created in this thesis must contain, to examine if the addition of haptics yields any additional benefit to pain relief. However as discussed in this chapter pure embodiment is not the only element which contributes to studies of Phantom Limb Pain but that of the sense of agency. Mirror box therapy has some effect but the fact that the affected arm is not making the movements which are being observed hampers the therapy's effectiveness. The use of visual or mechanical tracking along side amputated side grasp/release must be used to complement each other in order to provide as strong as possible levels in both embodiment and agency.

Chapter 7

System Architecture and Design

7.1 Introduction

This chapter presents the requirements and design of the system produced for the pilot clinical feasability study, drawing from technological based approaches discussed in chapter 5 and 6. First the requirements of the system are detailed before an overview of the system and it's individual components are examined in detail.

7.2 System Justification

Chapters 4, 5 and 6 have examined the different pain phenomena experienced during the amputation process, treatments after amputation for Phantom Limb Pain and Embodiment, agency and how it relates to Phantom Limb Pain respectively.

Erlenwien and colleagues [124] highlighted the two theories of Phantom Limb Pain that complement each other, those activity during phantom movements of the arm and reorganisation during tactile stimulation. This leads to visual feedback treatments in particular mirror box therapy, that traditionally due to the physical configuration has limitations in terms of viewing angles and movement of the non amputated limb. Using immersive virtual reality allows for the decoupling of mirror box therapy, the amputated limb moving with grasp and release being controlled via residual muscles to allow interaction between the participant and the virtual environment. This is important due to embodiment being an element that contributes to a reduction in post amputation pain, strengthen by correct anatomical representation of the missing limb visually along side synchrony between visual and tactile feedback. Traditional mirror box therapy involves movements of the intact arm in order to maintain engagement and for the therapy to have any possible effect. In order for the participant to maintain engagement, exercises which are designed to maximise interaction need to be designed to gamify the reach, grasp, transport and release paradigm

involving activity of daily living like tasks.

With this in mind, the system was designed taking into consideration the following:

1. A visual system delivered via immersive virtual reality to expand visual cues unconstrained by the physical limitations of the mirror box therapy setup. This facilitates scaling of movement for those individuals who might have movement limitations in order to replicate normal range of motion.
2. A system that provides tactile/ force feedback via a haptic robot to enhance visual feedback and the sense of embodiment which has previously been shown to have an impact on post amputation pain reduction[152][124]. The principle of force feedback aims to simulate the physics of interaction (such as the weight of an object, its shape, texture and collisions) of the user through a virtual avatar and an object within the environment.
3. A system that allows control of a virtual limb by movement of the residual limb tracked by a haptic robot which allows decoupling of the mirror box therapy and colocation of the physical limb virtually. The system in addition, provides weight support through a splint and gimbal mechanism. Movement accuracy is granted through several sensors that measure minute physical movements that translate to the virtual environment.
4. A system that allows control of the opening and closing of the virtual hand by the amputated side, in order to allow participants to interact with the system in a natural way.

The combination of these elements would allow a range of upper limb amputees who might also have additional injuries that restrict movement to engage with the system. Such a system can also be used early on in the amputation process, which Erlenwien and colleagues summarised in 3 out of 5 of the key points raised in their current review of Phantom Limb Pain; "From the clinical point of view, prevention should be focused on effective reduction of perioperative pain intensity and early restoration of the body scheme. Mirror therapy, proprioceptive training, virtual reality, and modern prosthetic and surgical approaches are the most promising approaches for the treatment of established phantom limb pain. Treatment should include multimodal approaches co- ordinated within an interdisciplinary team." [124].

7.3 Summary of requirements

As shown in the previous chapter technological based approaches to Phantom Limb Pain treatment have their benefits in terms of minimising side effects. It is clear that the use of immersive virtual reality must be considered in the system proposed by the thesis work, highlighted in Chapter 5 and also to maximise any benefit such a system can have on perceived levels of pain and maintaining any benefits. Equally clear is the need for correct anatomical positioning of the limbs to enhance embodiment and agency via muscle activation through EMG. Interacting with the environment not just with picking, transporting and releasing objects but utilising deeper interactions with haptics via force feedback.

7.3.1 User Requirements

User requirements of the system can fall into two categories 1) user comfort when using the system and 2) user expectations.

1. User Comfort:

- During the intervention the system hardware should not cause stress in terms of ill fitting or poor physical design.
- The environment in which the intervention is carried out should be clean, free from major noise and distraction.

2. User Expectations:

- The therapy exercises should be both rewarding and engaging whilst maintaining health and safety standards.
- In order to maintain participant engagement throughout the whole process of the session, tangible and useful data in the form of a score was used.
- The system should provide realistic expectations set out by medical staff with regards to the physical limitations of each user during therapy exercises.

7.3.2 Technical Requirements

The requirements are as follows:

- The use of immersive virtual reality.

- Anatomically correct inverse kinematics for both the amputated limb and intact limb in order to increate full immersion.
- A fully rendered avatar to aid in immersion by reducing any negative side effects that Phantom Limb Pain suffers might experience if incorrect postures etc are present, so to eliminate the "floating hand" problem faced by many immersive virtual reality systems currently available.
- Provide biofeedback to increase the level of agency and functional embodiment that the participant experiences.
- Provide force feedback to also further increase levels of functional embodiment and agency.
- The ability for the user to stop the system in any state of execution should be given in both software and hardware format.
- The whole system should be modular in that components should be exchangeable in the event of improvement and expansion. An example of this could be the implementation of a new Haptic API, which could replace the current API.
- The system should be as immersive as possible in order to provide the user with an effective embodiment of their projected virtual limb.
- The system should be capable of kinematic tracking/mapping of the intact arm and residual limb to a virtual surrogate.
- The system should be able to detect grip formation and release.
- The system should utilise multiple psychophysiological sensors in order to gauge stress and feelings of pain that the user might experience whilst using the system.

7.4 Overview of the System

The system was designed based on the user and technical requirements to allow motor tasks to be performed using an immersive haptic sensorimotor training system that provides, direct physical contact to a haptic robot, mapping of the information from the robot to the virtual representation of the physical limb, and applications in terms of exercises that maintain challenge and interest to the individual. Based on these elements, the system acquires EMG commands, residual limb kinematics and displays the combined residual limb movements

in a virtual reality environment that includes force-based interactions with virtual objects. Visualisation is provided via a HMD so as to facilitate first-person view of the virtual environment and embodiment of the residual limb with the virtual representation. Unreal Engine 4 is used to render the exercises together with custom software that synchronises the control loops and communication with the different subsystems. An example of a participant using the system can be seen in Figure 7.1.

Here we can see a right sided amputee participant during a session with their residual limb attached to the gimbal and robot also wearing the HMD. Behind the participant the main computer's monitor can be seen displaying the participant view point while interactions with the box and blocks style exercise, below displaying their filtered EMG signal can be observed with the black box displaying an image of the classified EMG output, either grasp or release.

The system therefore meets the design specifications mentioned above by combining the core elements "Feel, Control and See" (Figure 7.2).

Figure 7.1: Participant using the system during the clinical feasability study.

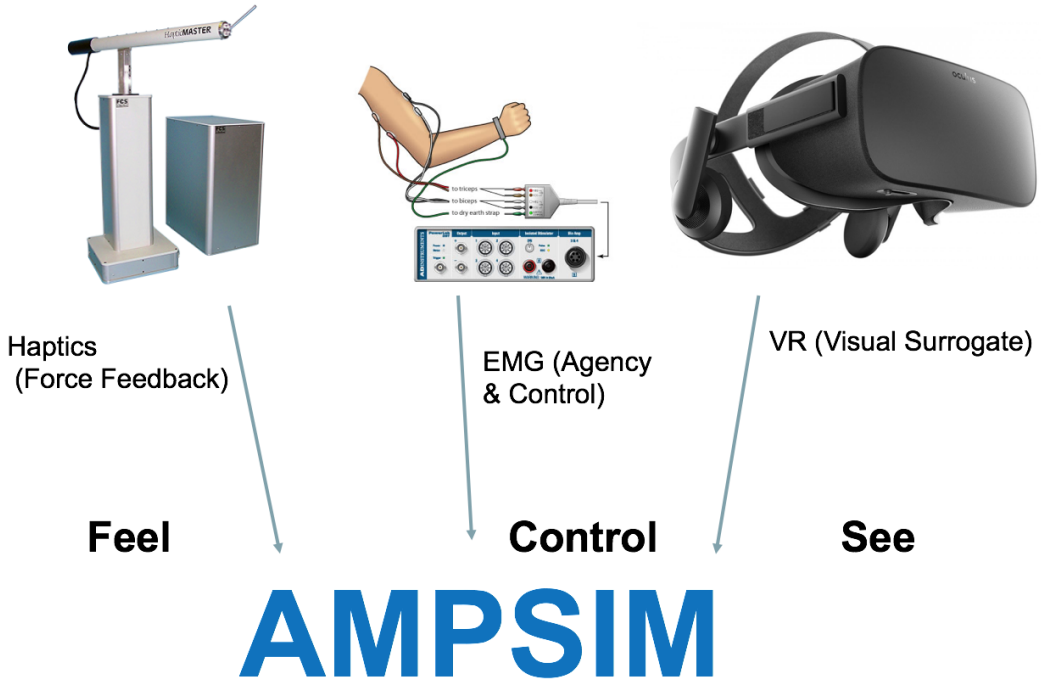


Figure 7.2: AMPSIM Concepts

What Figure 7.1 shows can be summarised conceptually by Figure 7.2. The participant sees the environment and anatomically corrective limb position immersively via the HMD acting as a visual surrogate. The classified online EMG data allows the participant to open and close the virtual hand enhancing agency and facilitates control over the objects within the virtual environment. Finally the participant's residual limb is attached to the six DOF haptic robot allowing not just direct mapping of the physical limb to the virtual limb in both position and orientation but also provides force feedback from interactions between the environment , the objects within it and the residual limb.

What follows in the rest of this chapter is an overview of the various components implemented.

7.5 System Architecture

Figure 7.3 provides an overview with the user in the loop and Figure 7.4 shows a block diagram of the system with arrows indicating the flow of data inside separate parts of the system. Figure 7.4 also includes the types of data which are exchanged within the system and the specific software used.

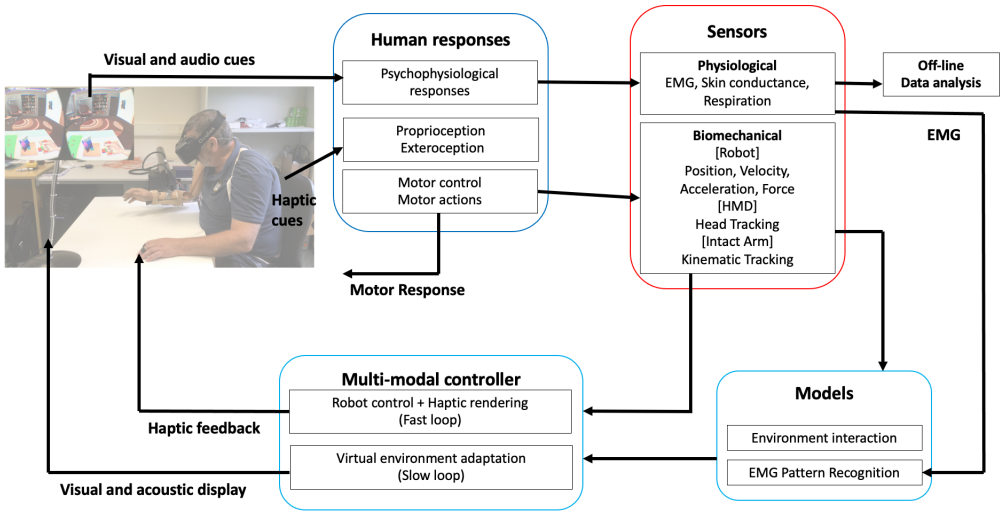


Figure 7.3: Overview of the system architecture showing the flow of information between the different areas of the system.

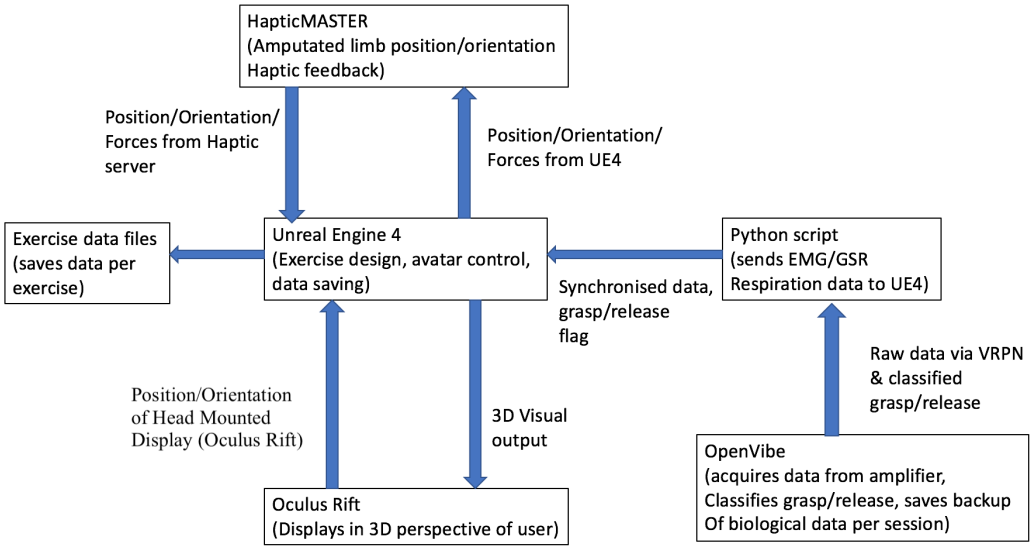


Figure 7.4: Block diagram showing the overview components of the system and the data that flow between them.

As shown in Figure 7.3 the system architecture is represented as a closed-loop system where the loop is closed around certain human responses while interacting with a virtual task, primarily using EMG to grasp and release objects. Such components are characterised by four main modules:

- **Human Responses:** represents the participant's interaction with the system. The resulting data that is sent via the sensors is fed back into the system (via the controllers). These human responses to events during the exercises are logged and are used as event triggers in the offline analysis of the data.

- **Sensors:** the sensors capture human responses. Physiological sensor information is used to quantify psychophysiological responses to the audio-visual and haptic cues provided by the system. Perception of the environment (and from the haptic cues) will invoke proprioceptive and exteroceptive user responses that will result in motor actions and a subsequent response (e.g. movement of the limb). Motor control actions are picked up by a range of different biomechanical sensors present in the robot, by the HMD and kinematic tracking of the intact limb.
- **Models:** representations of the environment interactions are used to define behaviour and interaction paradigms (e.g. object to change colour when touched), EMG pattern recognition helped identify motor intention (e.g. move limb, open hand) as well as the continuous online data analysis.
- **Multi-modal controller:** the control and interaction loops close around a multi-modal controller consisting of a fast loop (control and haptic rendering) for haptic feedback and a slow loop (virtual environment adaptation) for audio-visual feedback. The virtual environment in which the exercises take place is located in this module, along with the haptic effects, which change the parameters of the environment.

This section provides further detail to the system architecture summarised in the previous section by braking down each oof the subsystem components.

7.5.1 Human responses

Human responses are invoked during the process of using the system. Picked up by the sensors they refer to the human output from the resulting input of visual, audio and haptic cues. An example of this would be how the participant would respond to the haptic cue of feeling an object in the virtual environment. The response to the interaction would be fed back into the system to alter the multi-modal controller acting as external trigger to modify the system's state. The main data analysis focuses on the responses exhibited during the sessions collected from the sensors into the session files.

7.5.2 Sensors

In order to register and act on the human responses while users interact with the exercises, an array of different sensors is required (both physiological and biomechanical). This

includes a combination of off-the-shelf products and custom made sensors in order to meet the requirements. Physiological sensor information is used to quantify psychophysiological responses to the audio-visual and haptic cues provided by the system. Perception of the environment (and from the haptic cues) will invoke proprioceptive and exteroceptive user responses that will result in motor actions and a subsequent response (e.g. movement of the limb, feeling the weight of an object). Motor control actions are picked up by a range of different biomechanical sensors (present in the robot), by the HMD (head tracking) and kinematic tracking of the intact limb. The following section summarises the requirements and compares a number of physiological and biomechanical sensor systems.

7.5.2.1 Physiological

Physiological sensors monitor information related to the users biological state. Galvanic skin response (GSR) and respiration rate were chosen to measure the psychophysiological responses to the training regime. EMG is selected to record muscle activity and detect grip formation and release in the residual limb using simple EMG pattern recognition methods.

Sensors were selected to fulfil the following requirements:

- Must meet medical/safety standards.
- Ideal to be non-intrusive.
- Must be comfortable to wear.
- Must allow for a quick set up time before experiments.
- The sensors must be durable enough to withstand the rigors of physical exercises and to last the duration of the project.
- Must provide access to SDK in order to manipulate data, and to be able to be accessed by the robotic system.
- Must be compatible with open source analysis tools such as OpenVibe.
- Ideally sensors should use the same amplifier from one manufacturer to ensure data consistency, common signal to noise ratio and avoid possible synchronisation issues with other sensor data.

The steps necessary to detect grasp and release is summarised in Appendix D.2. OpenVibe was chosen due to support from a range of amplifiers and the ease of programming and

support needed to classify the online data. OpenVibe also supports VRPN [206] which was used to send the classified grasp or release data to the virtual environment adaption loop.

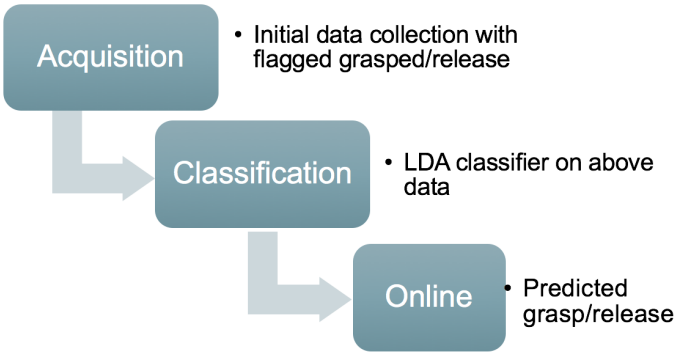


Figure 7.5: Flow diagram showing the steps required to classify EMG signals for grasp/release within OpenVibe. During the acquisition stage data is collected and marked as grasp or release.

The use of OpenVibe allows full control for opening and closing of the amputated hand virtualy as discussed in chapter 6.

The amplifier used for the thesis work was the TMSi Porti 32 channel amplifier with bipolar electrodes for the sensors and a unipolar electrode for the ground. The TMSi was chosen due to the compatibility with OpenVibe, Figure 7.6.

Figure 7.6: The TMSi Porti 32 channel amplifier

For more information regarding OpenVibe please see appendix D.1.1.

7.5.2.2 Biomechanical

This module details the biomechanical sensors, which were used within the system. Unlike the physiological sensors, biomechanical sensors provide output from the system as well as input into the system. For example the HapticMaster haptic robot (as shown in Figure 7.1) inputs position data from the residual limbs and outputs haptic effects and the HMD

inputs head movement and outputs video.

In order to select suitable biomechanical sensors needed for this project the following requirements have to be taking into consideration:

- The biomechanical sensors must meet health and safety requirements in order to be used for the feasibility clinical study.
- As with the physiological sensors, user comfort is an extremely high factor when choosing biomechanical sensors.
- The sensors must be durable enough to withstand the rigors of physical exercises and to last the duration of the study.
- The use of such sensors/actuators should involve as little set up time as possible to ensure user comfort.

7.5.2.3 Haptic Robot

The HapticMASTER developed by FCS Control Systems shown in Figure 7.7 comprises two parts. The robot arm which houses the force sensor, end effector (to which a gimbal is placed on the system) and the three actuators which provides the kinematic chain. Figure 7.8 shows the first actuator provides rotation around the base of the unit, the second actuator provides vertical movement and lastly the final actuator provides movement towards and away from the unit. This provides the end effector (located at the furthest end away from the unit) with the three degrees of freedom. The HapticMASTER is an admittance control haptic device (force in, and displacement out) as opposed to an impedance controlled haptic device (displacement in, force out) which results in a large workspace as shown in Figure 7.9. Specifications of the HapticMASTER can been seen in Table 7.1.

Specifications of the HapticMASTER	
Property	Value
Workspace Area	$80.10^{-3}[m^3]$
Position Resolution	$4.10^{-6} - 12.10^{-6}[m]$
Maximum Force	$250[N]$
Maximum Velocity	$1.0[m/s]$
Force Sensitivity	$0.01[N]$

Table 7.1: Selected specifications of the HapticMASTER Robot

The HapticMASTER's large workspace makes it suitable for arm movements during the sessions. One benefit with using an immersive virtual reality paradigm with a HMD is that

movements from the HapticMASTER can be scaled in each axis, providing the participant the full experience of moving the virtual arm around the environment despite any issues in range of movement from additional injuries which could break the illusion of controlling the arm if immersive virtual reality was not used.

The robot arm unit is connected to the control box which houses the haptic server, amplifiers for the actuators and also the network connection which acts as the input/output to the main computer. The haptic server is in control of two main functions, the haptic renderer and the control loop for the actuators. These two functions run at 2500Hz. This is necessary in order to create believable haptic effects. Which in addition to virtual springs can via the haptic API support different kinds of geometry and effects.

A plugin for Unreal Engine 4 acts as the communication between the haptic server and the main computer using shared memory. This uses the .dll file provided by the HapticMASTER API. The HapticMASTER is fully CE marked for use in medical research, making it ideal for the system.

The HapticMASTER was used for the system due to the research group's experience using it with previous work in rehabilitation robotics for different patient populations and the size of the workspace provided by the HapticMASTER. To facilitate 6DOF within the system; a 3DOF gimbal was used produced by Moog [1] as shown by Figure 7.10 with the residual limb interface attached to the base plate of the gimbal.

[1] https://www.moog.com

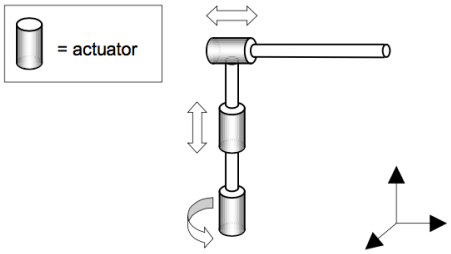


Figure 7.8: The kinematics for the HapticMASTER

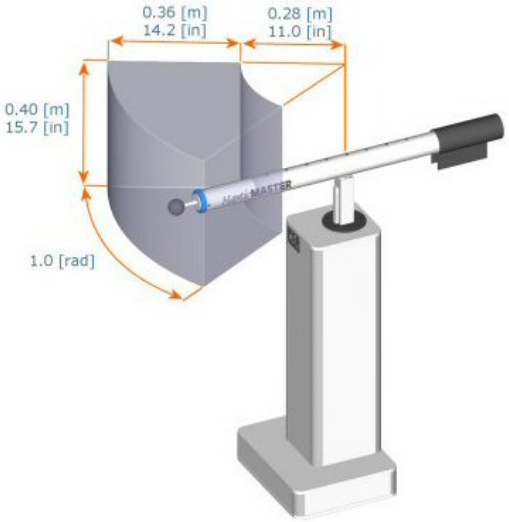


Figure 7.9: The HapticMASTER workspace overview, with end effector represented as a grey ball.

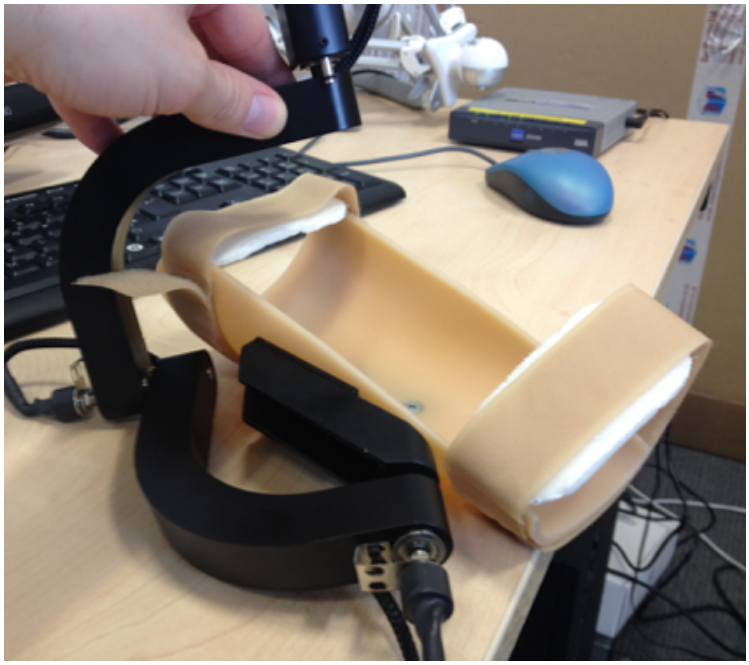


Figure 7.10: 3DOF gimbal used in the system

The gimbal is considered to be a "Activities of Daily Living (ADL)" gimbal due to its design, unlike a more traditional gimbal such as one featured on Figure 7.11. The ADL gimbal does make integrating it within a tabled environment easier at the cost of exposed pot sensors which might get damaged.

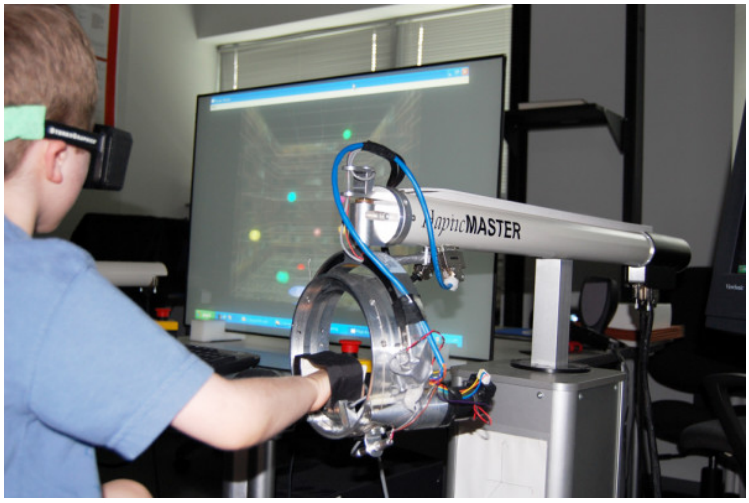


Figure 7.11: Traditional "Ring" type gimbal used on a HapticMASTER

The gimbal axes correspond to the individual potmeters. Potmeter 2 measures yaw orientation located at the top nearest to the end effector. Next, potmeter 1 measures pitch and lastly potmeter 3 measures roll. This results in a yaw, pitch, roll configuration (right-handed) for the participant's amputated limb. The kinematics of the gimbal can be seen in Figure 7.12.

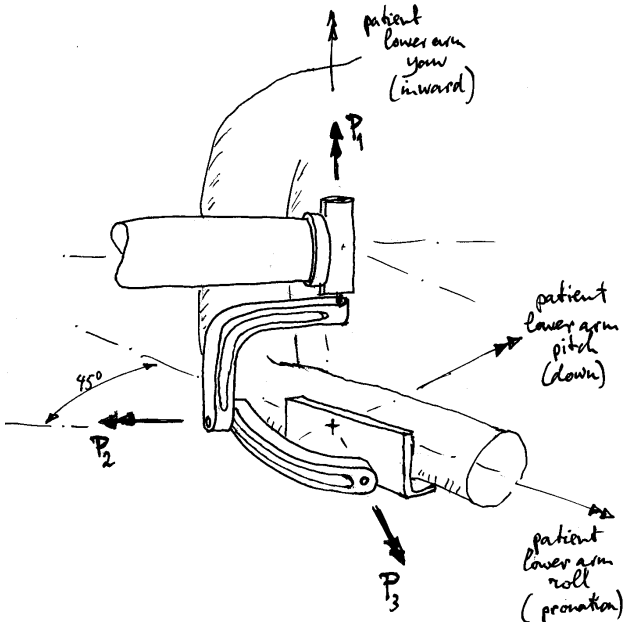


Figure 7.12: Hand drawn diagram from Moog showing the kinematics of the ADL gimbal

The potmeters have to be calibrated to ensure correct Euler axis conversion. For an

in-depth examination of the gimbal including the Euler axis conversion used within the system, please see appendix D.1.3.

7.5.2.4 Head mounted display and head tracking

The sole visualisation for the participant is provided by the Oculus Rift HMD [2]. Secondary visualisation is provided in 2D on the main computer's screen for the sake of the experimenter to see what the participant is viewing to allow feedback.

During the process of development various versions of the Oculus Rift and the Sony 3D headset were used. However for the clinical feasability study the Oculus Rift DK2 (Development Kit 2) and CV1 (Consumer Version 1) versions were used.

Unreal Engine supports a number of HMDs from Oculus to HCT, however due to the spacial requirements the Oculus Rift was used. For more technical information please see appendix D.1.2.

7.5.2.5 Intact arm tracking

The main benefit of using the Oculus Touch Controllers (as shown in Figure 7.13) is the built-in integration into Unreal Engine. The handheld units supply the position and orientation data of the individual unit via the same infra red camera tracking the head set and also analog button presses and gestures. Due to the single camera usage for both the headset and touch controllers the positional and orientational data derived from the controllers is very accurate in relation to the position of the headset.

Figure 7.13: The Oculus Touch controllers

[2] https://www.oculus.com/rift/

7.5.3 Models

7.5.3.1 Environmental Interactions

In order to create the virtual environments and resulting interactions, Unreal Engine 4 was used. The environment section of the editor allows free movement in 6 degrees of freedom within the constructed virtual environment, with objects dragged from the content window into the environment to be placed and manipulated. Various elements such as the scale, rotation, position, material properties etc can be changed in the inspector window per object placed within the environment.

Environmental interactions regulate all the interactions within the virtual environment. Examples of these interactions include:

- Built-in physics engine that includes collision meshes, forces, joints, and motors. This part is heavily connected as well with the haptics part of the systems, since the meta-data being used to dictate the physical aspects of objects will be fed into this module to provide physical properties to objects. An example of these types of interactions includes weight values of say a glass of water to provide a dynamic feel to the user when handling such objects in the virtual environment. These properties can be passed onto the spring and dampener values to simulate these effects. The collision mesh elements of the engine provide simplified methods to access code and ability to successfully implement haptic effects within the system.
- Also using built in features of Unreal Engine 4, the lighting engine is utilised to provide correct and real time lighting (ray tracing, shadowing, etc) to the virtual environment. An example of this would be the virtual manipulation of objects by the user displaying the correct real time shadows and lighting. This ensures that the 3D aspect is free from error and also makes the environment more immersive.
- Although not part of Unreal Engine, the haptic effects are a form of environment interaction. These haptic effects are delivered using the HapticMaster API (and added later via either custom written effects, from different Haptic APIs). Examples include spring effects for weighted objects and magnetic fields, which can be used to assist users reach. Also simple geometrical shapes such as cubes, spheres and cylinders can be quickly created within the haptic API.

- Another environment interaction, provided by Unreal Engine 4 and by the HMD is the stereoscopic image seen by the participant. Unreal Engine provides the 3D effects in software form but the HMD compiles that output and displays the data as a stereoscopic image.

Unreal Engine 4(UE4) developed by Epic Games is primary designed as a game development tool. UE4 provides a view to the virtual environment in three dimensions, access to imported objects to place in the environment and access to blueprints. Blueprints are the visual scripting method used within UE4 and allow quick construction of logic using prebuilt libraries provided by Epic Games as well as custom written libraries created by 3rd party developers.

The environment section of the editor allows free movement in 6 degrees of freedom within the constructed virtual environment, with objects dragged from the content window into the environment to be placed and manipulated. Various elements such as the scale, rotation, position, material properties etc can be changed in the inspector window per object placed within the environment.

Blueprints allow quick visual access via flow type programming allowing the user to apply logic to objects such as setting variables, getting user input etc. This is achieved by associating flow boxes to events such as "Event Tick" which fires 1000 per second whilst the application is running. This simple style of programming is suited to complex 3D programming due to instant feedback and running of simulations within the editor.

7.5.3.2 EMG pattern recognition

OpenVibe, initially a Brain Control Interface (BCI) software was developed in collaboration with Inria Rennes and partners, comprised of two parts, an acquisition server and a programme designer. Due to OpenVibe's open source nature the software is ever evolving both in devices supported and features available to the user when designing programmes.

The acquisition server allows connection to a vast and growing range of acquisition devices such as g.tec, Brain products, OpenEEG and TMSi devices to name but a few. The open source nature also allows users to write drivers for acquisition devices not yet supported. The communication protocol such as USB, Bluetooth or WiFi can be selected as well as the sampling frequency and sample count per sent block from the device to the OpenVibe designer.

The OpenVibe designer is used to programme custom made software to access the raw data from the acquisition server and to process the data to perform such tasks as classifying signals etc.

OpenVibe offers a small number of classifiers to be used via the classifier trainer box, Linear Discriminant Analysis and Support Vector Machine based classifiers, both examples of labelled, supervised classifiers due to the nature of the simple usage and data collection.

The Classifier Trainer box is a generic box for training models to classify input data. It works in conjunction with the Classifier processor box. This box's role is to expose a generic interface to the rest of the BCI pipelines. The box will generate an internal structure according to the multiclass strategy and the learning algorithm selected.

The behaviour is simple, the box collects a number of feature vectors. Those feature vectors are labelled depending on the input they arrive on. When a specific stimulation arrives, a training process is triggered. This process can take some time so this box should be used offline. Depending on the settings you enter, you will be able to perform a k-fold test to estimate the accuracy of the learned classifier. When this training stimulation is received, the box generates a configuration file that will be usable online by the Classifier processor box. Finally, the box outputs a particular stimulation on it's output, that can be used to trigger further treatments in the scenario.

Due to the low number of features extracted which are required for classifying basic grasp and release two dimensional Linear Discriminant Analysis was chosen and is detailed in appendix D.1.4.

In order to provide natural grasp and release, the output of the classifier file was regarded as successful if the accuracy was 75% or above. Any classifier below 75% required the participant to perform another round of data acquisition to reclassify, or to use another muscle group to improve accuracy.

7.5.4 Multi-modal controller

The multi-modal controller module contains the two loops (as shown in Figure 7.3), which constantly run whilst the exercises are taking place. Input from both the sensors and software are feed to the loop and processed. These loops have to be run at two speeds, a fast loop (Robot control + Haptic rendering) and a slower loop (Virtual Environment Adaption).

The reason for these two speeds will be explained in the below subsections.

7.5.4.1 Robot control and haptic rendering

Robot control and haptic rendering is performed using closed-loop control techniques. Arm movements and haptic effects are delivered via the HapticMaster using sensor information from the system (positions, forces, EMG commands, etc as shown in Figure 7.3). The reason why this loop is a fast loop is to ensure reliable movement control and haptic effects are produced with minimal user perceptual sensation discrepancy. The controller runs in real-time closing the loop around the HapticMaster motor amplifiers and sensors using the VxWorks RT Operating System. Both the robot control and haptic rendering run at a fixed frequency of 2500 Hz, hence the fast loop ensuring that both the robot control and haptic rendering are optimal constantly. Figure 7.14 shows the outline of the loop taken from [207].

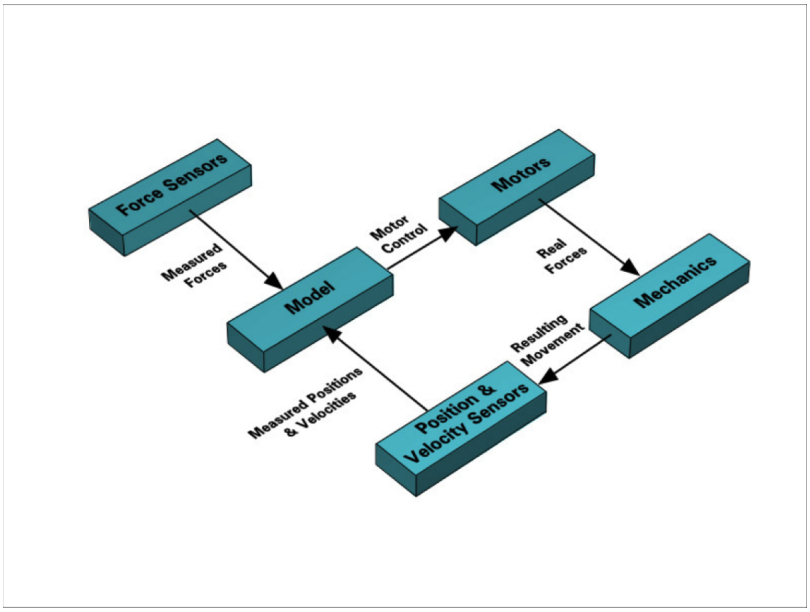


Figure 7.14: The fast loop of robot control and haptic rendering. Extracted from [207]

Figure 7.14 can be summarised by the following procedure:

- Read the force sensor (located in the end effector) to show external forces exerted by the user (e.g the input).
- Add all virtual forces due to virtual objects and effects (from the software and slow loop).
- Calculate the resulting virtual motion in the virtual model module.
- Using the motion calculated, command the HapticMaster to move according to the

calculations (e.g the output).

What is needed is an efficient algorithm for haptic rendering and for simulating friction between surfaces. As a result the the GOD object algorithm was chosen for haptic rendering due to its high speed and established use in haptics research, along with previous research [208] which used these algorithms with the HapticMASTER. This combination of prior specific usage and established research lead to the decision to implement these two algorithms within the system detailed below.

GOD object algorithm

First published by Zilles et al in 1995 [209] in order to solve the problem of the simplifying calculations needed for haptic rendering for complex geometry, introduced the haptic interaction point (HIP) which is defined as the physical endpoint of the haptic device interacting and penetrating correctly with virtual objects. Zillies highlights two issues facing this problem; multiple objects and thin objects are both examples.

Multiple objects pose a problem for haptic algorithms due to the regions of overlapping sections of the virtual object are present. When the operator of the haptic device is in contact with multiple objects at the same time the total stiffness could possibly be greater than either surface of the objects. This poses issues in modelling complex/multiple objects due to the complexities which in total could exceed the maximum stable stiffness of the haptic device.

Thin objects also pose a problem for haptic algorithms due to the need for the HIP to travel at least some distance into a virtual object for forces can be calculated and applied to prove the object with a sense of touch. This is due to variable servo and mechanical stiffness found within haptic devices. Issues include when the distance the HIP has to travel in order to calculate the forces becomes much greater than the thickness of the object being interacted and produces incorrect forces. When the HIP reaches half way through the object it is pulled the rest of the way and the vector field algorithm calculates that the user has approached the virtual object from the opposite side. A simple solution would be to keep a record of contacts between the HIP and any virtual objects with meta data providing the correct forces etc to be applied. However this potential solution would slow the speed of the algorithm and would become processor intensive.

It was for these two reasons that this algorithm was created. Using Lagrange multipliers

to calculate the new location of the god object during contact with a virtual object, this new point is calculated to be the point at which the distance between the current god object point (GOD) and the HIP, with any constraints calculated so that correct motor commands can be sent to a haptic device. In practical terms the GOD object is the calculated (with constraints and other variables) representation of the virtual HIP where the HIP would be if the object was infinitely stiff. As such the GOD object travels beyond the surface of virtual object so to ensure the direction of force is always clearly calculated. These elements thus provide far more appropriate and realistic forces when touching and colliding with a virtual object along with solving the two problems of multiple objects and thin objects.

When no collisions or sustained contact with a virtual object is present both the HIP and GOD objects should be co-located. When such collisions or sustained contact is detected the GOD object will remain on the surface of the virtual object with this distance between the HIP and GOD objects being minimised. The GOD object moves across the surface of the object if no friction is present, however friction can be implemented separately which will be mentioned later. State variables are also constructed for the GOD object including the DOFs of the haptic device being used so that appropriate measures can be calculated and applied to the haptic device. After the GOD object's location within a virtual environment has been calculated the resulting force can be calculated by impedance control methods listed in subsequent sections of this chapter. In order to simulate virtual object material properties such as softness etc, stiffness values along with damping values can be applied between the HIP and GOD objects to provide such sensations as softness and deformation. This is achieved using triangular meshes due to the fact that the algorithm is only concerned with the surface of the object and triangular meshes can be moved in real time and still retain correct geometrical surfaces along with allowing deformable surfaces when correct forces are applied. One additional major benefit of using triangular meshes is for their simplicity when it comes to collision detection providing one way constraints when applied to an infinite surface when detecting penetration (positive distance if the GOD and HIP location is near or nearly touching an object's triangular mesh, negative distance if the HIP is on the other side of the mesh). When the surfaces of a virtual object are not infinite, individual surfaces can be made active and in addition a subset of conditions can be invoked

such as ensuring that the GOD object contact must be within the boundaries of that surface mesh; this is achieved by line tracing from the old GOD object position to the new HIP and ensuring the line passes through the mesh making it active.

For more complex objects such as spheres or convex objects the GOD object algorithm ensures that only one surface mesh is active at one time.

How this is achieved is visually represented in Figure 7.15, with the small dot representing the location of the HIP and the larger dot representing the location of the GOD object. What the figure demonstrates is the two step procedure between movement the two surfaces with a) showing the approach of the left hand side of in this case one side of a cube, b) this previous side of the cube still being active so that calculations for the GOD object can be computed and the GOD object moved appropriately. Finally c) in which now the GOD object is clear of the left side of the cube it can be placed on the right hand side, with appropriate forces being sent to the haptic device.

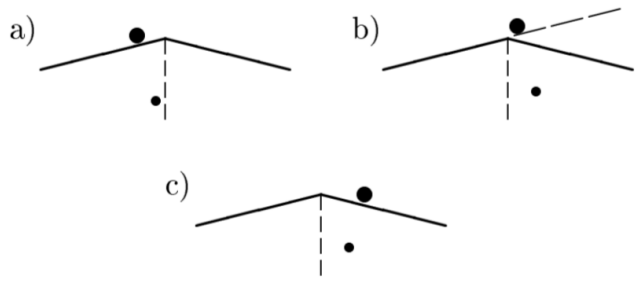


Figure 7.15: How the GOD object algorithm handles convex virtual objects. Extracted from [209]

Firstly the GOD object is placed over the surface of the second object/mesh but still in the plane of the first object/mesh, as the GOD object is used purely for calculation the object can be located in a plane of an object/mesh. The next step involves the servo loop within the algorithm and in the next servo loop the first mesh will no longer be active giving the ability for the GOD object to move to the second mesh. Due to the relatively small distances and time from the first step and the next modification of the shape is limited.

Friction Cone Algorithm

In 2002 Harwin and Melder[210] provided an update on the GOD object algorithm to include multi finger haptic environments and also to model friction.

Friction does play a greater part in multi finger/point systems and in fact is vital when manipulating virtual objects haptically in an accurate manner with correct forces being

applied back to the user. Friction is needed for manipulating objects in position with gravity and rotating said objects, again with correct forces of friction applied.

Harwin and Melder highlighted 3 core aspects when implementing friction into a multi-point environment [210]:

1. identification of collisions
2. an estimation of external forces resulting from the collisions (including frictional forces)
3. an appropriate response to the residual forces.

The core element of the friction cone algorithm is the HIP, in that the HIP determines were the cone is located which poses issues when the algorithm is used in its intend purpose which is multi-point environments involving multiple HIPs. Object manipulation with more than one HIP requires multiple forces acting on the object/mesh. This is solved by summing all the forces which are stored as vectors providing a final residual force for that given object/mesh.

Residual torque is generated due to these resulting force moments at the point of the virtual object's centre of gravity. As per previous forces, this torque is stored in a vector which can be used to implement how the virtual object reacts physically to the final applied force. This also applies to other physics based variables which can be derived from the virtual object such as the centre of mass and moments of inertia and allows correct calculation of gravity and rotational forces. Gravity is simply a vector force with just the third variable set in the z axis and rotational forces are calculated via moments around the virtual object's centre of mass.

For a mathematical description of the GOD object and friction cone algorithm please see appendix D.1.6.

7.5.4.2 Virtual environment adaption

The virtual environment adaption module (slow loop) refers to the visualisation of the exercises and the visual changes which occur during the execution of the exercises (as shown in Figure 7.3). This module also contains the interactions between the sensors/ models and the fast loop (robot control and haptic rendering). The interchange of data from these two sub modules in the multi-modal controller is facilitated by the plugin, which allows the graphics render of Unreal Engine to co-operate with the haptic render of the

HapticMaster. Input into this module comes from the human responses and the 'models' modules. The output generated by the virtual environment includes the change of state within the current exercise being executed. For example if the user is tasked with reaching and grasping a cube, the following actions within the system take place:

- When the user moves to pick up the cube, kinematic data is obtained from the intact and residual limb using a combination of visual (Oculus Touch, Figure 7.13) and kinematic tracking (HapticMaster).
- When the user grasps the cube using EMG pickups, the information is passed into Unreal Engine to render the closing of the hand visually. Once the cube is grasped, the object properties (inc. mass and current location) are computed to generate appropriate haptic effects to be rendered by the HapticMaster robot.
- Realistic and immersive interaction is achieved by synchronising the graphics and haptics loops.

These interactions can be built up together to form the foundations of exercises within the system.

7.5.5 Exercises

Participants in the study performed (virtual) tasks designed to facilitate unilateral and bilateral movements Figure 7.17. These tasks were located in different settings such as a virtual supermarket, outdoor area and a home setting. The tasks were designed to promote motor learning and also where possible, double up as assessment. Exercises are based on scenarios which are to be considered daily living tasks based on object manipulation. A sample of these exercises include:

1. An adaptation of the original 'box and blocks test' (BBT) [211] in a home environment. The version constructed for the clinical feasability study is modified to remove the walls of the box to allow those participants with reduced mobility to complete the exercise. E.g those with little or no vertical movement in their arm. Figure 7.16.
2. A task that involves cleaning dust from a painting to reveal the painting. This involved participants reaching towards a virtual eraser and maintaining a grasp using planar movements with the eraser to clean the dust.

3. A task that involves being located in a supermarket environment with a conveyer belt that carries food related objects for the participant to reach, grasp and transport to a shopping basket.
4. A task that involves laying a table with different arrangements in a restaurant environment.
5. A juicing task involving reaching and grasping fruit on a tree next to a juicer and putting fruit into the juicer in an outdoor environment.

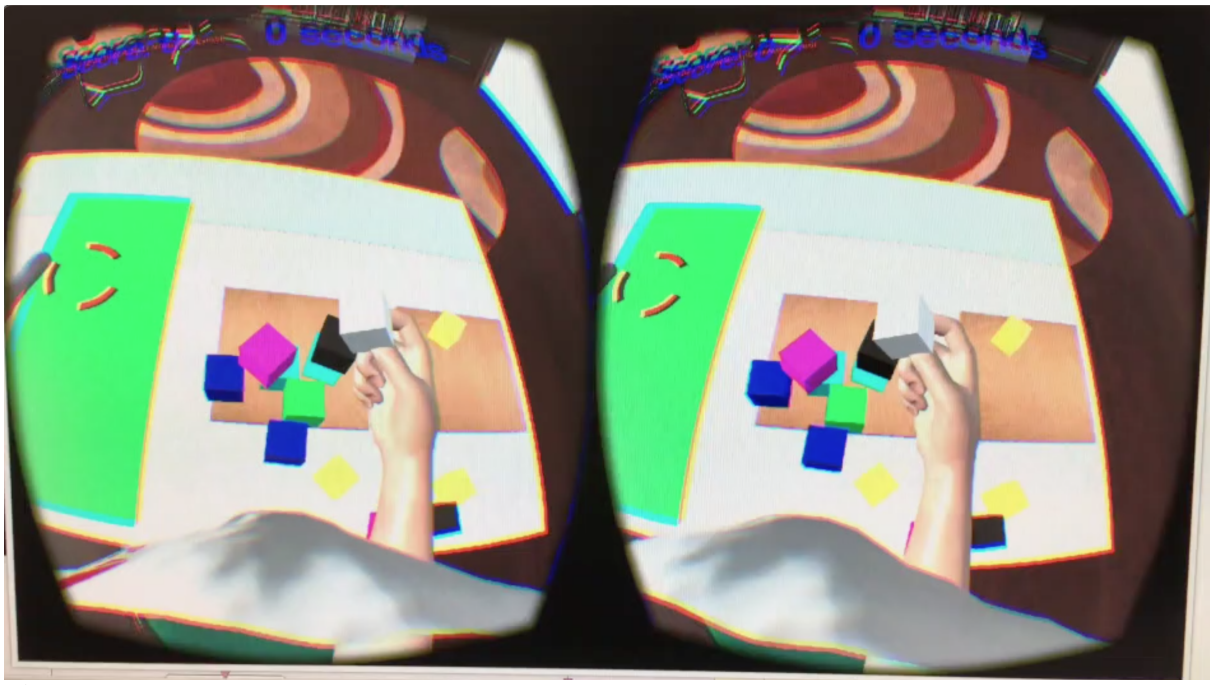


Figure 7.16: Right handed amputee participant view whilst using the system and interacting with the box and block test style exercise.

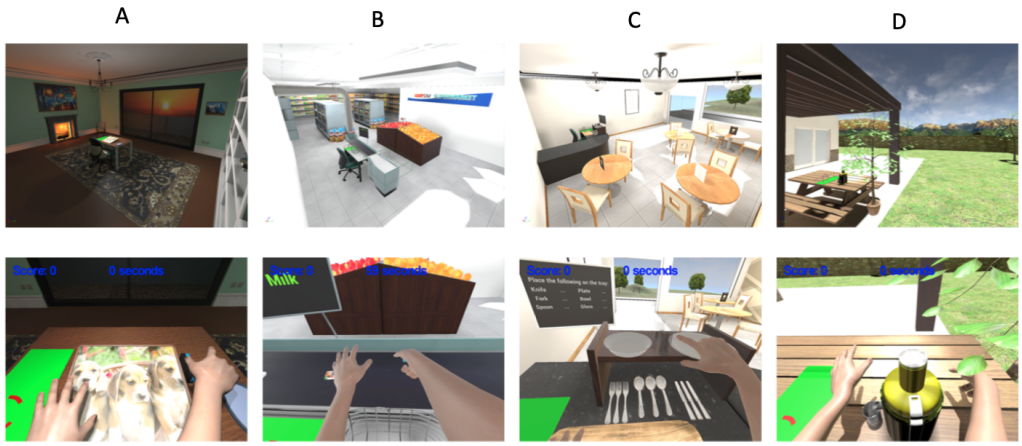


Figure 7.17: Example tasks and environments. Column A showing a home based environment and cleaning task, Column B showing a supermarket environment and a shopping exercise, Column C showing a restaurant environment with a laying the table exercise and Column D showing an outdoor environment with a juicing exercise.

These exercises have been chosen in order to gamify reach, grasp, transport and releasing of objects within the environment [208].This can then be expanded on in various ways shown by Figure 7.19 by modifying each step to make the exercises more engaging or challenging.

Figure 7.18: The standard box and blocks test showing the two sides separated by a divider. Taken from [212]

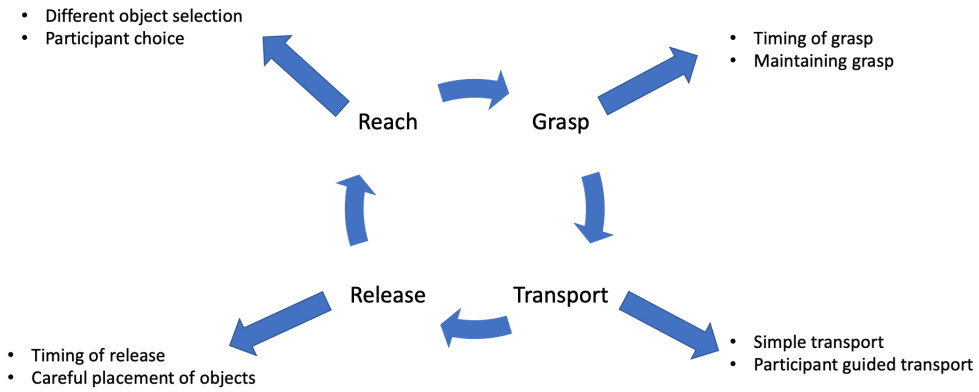


Figure 7.19: Gamification of the reach, grasp, transport and release paradigm but with additions to each section in order to engage the participants enabling the different exercises.

For example, the exercise based on the box and blocks test (Figure 7.18 allows the participant to freely choose the block to interact with. This figure shows the standard box and blocks test (BBT) arrangement. In that the participant is required to move as many coloured blocks from one side to the other within a given time.

The BBT due to it's simple set up can be modified in such a way in order to increase cognitive load. For example, the clear side of Figure 7.18 could be designed so that blocks have to be placed in a certain colour order or position. This would require complex transportation and release of the block. Yet the core elements of reach, grasp, transport

and release paradigm are still present, but modified.

For the system the BBT style exercise created, allowed the participants to grasp, transport and release blocks from one side to the other, but also provided participants the ability to stack the blocks on top of each other to add an extra layer of interaction to the exercise whilst still maintaining the loop in Figure 7.19.

7.6 Human Machine Interaction Diagrams

7.6.1 Inner Loops Synchronisation

Figure 7.20 provides a high level overview of the two main loops and individual system components as show in Figure 7.3.

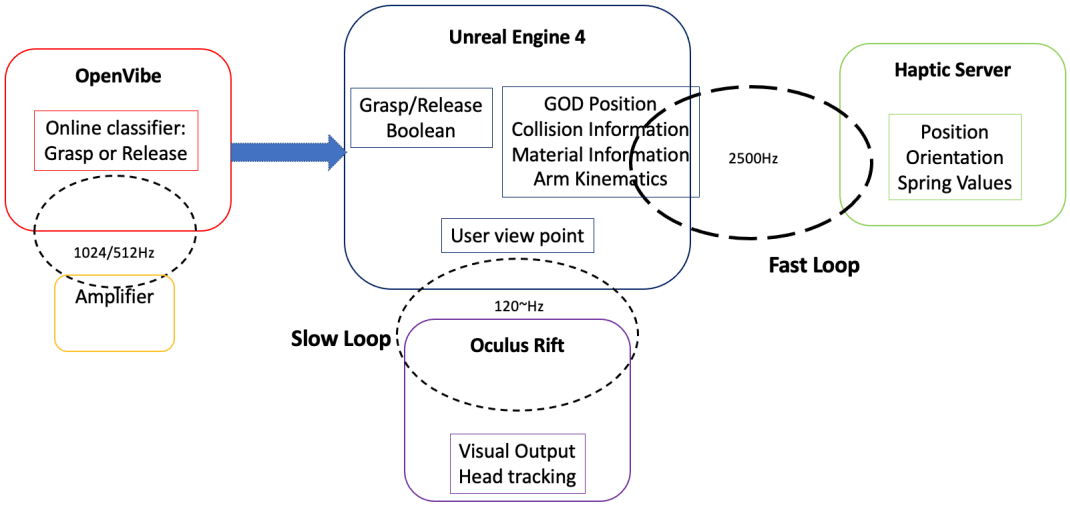


Figure 7.20: Loop flow diagram overview showing the two main loops in the system and how they interact with Unreal Engine.

The fast loop running at 2500hz can been seen inbetween the Haptic Server and Unreal Engine 4. This loop transfers positional, orientation and spring values to and from Unreal Engine to the Haptic Server. This in turn provides arm kinematic data needed for the inverse kinematics. As per section 7.5.4.1 the data from Unreal Engine 4 and the Haptics Server are exchanged in order to set the motor commands to facilitate control of the robot resulting in force feedback.

The slow loop which runs at 120Hz or approx 60 frames per second allows the visual environment to update. This includes outputting the user view point to the Oculus Rift but also relating the head tracking data from the HMD to Unreal Engine 4 to allow the correct

user view point to be updated.

In addition to the two loops, one other loop can be observed between the amplifier and OpenVibe. This is set at 512Hz via Bluetooth.

7.6.2 Human Movement

This section details interactions which takes place during the sessions. The communication between the sub systems is handled via plugins.

7.6.2.1 Grasp and release

One of the main ways the system allows interaction between the participant and the overall system is facilitated via grasp and release, shown in Figures 7.21 and 7.22 respectively. These two actions involve three sub systems of the whole system; OpenVibe for online EMG classification, the Haptic Server to send kinematic data of the amputated limb and also provide force feedback and Unreal Engine which acts as the main driver for these two sub systems. It should be noted that a Boolean can be set for the two groups (those experiencing visual and haptics, and those experiencing just visual) in order to apply haptic feedback.

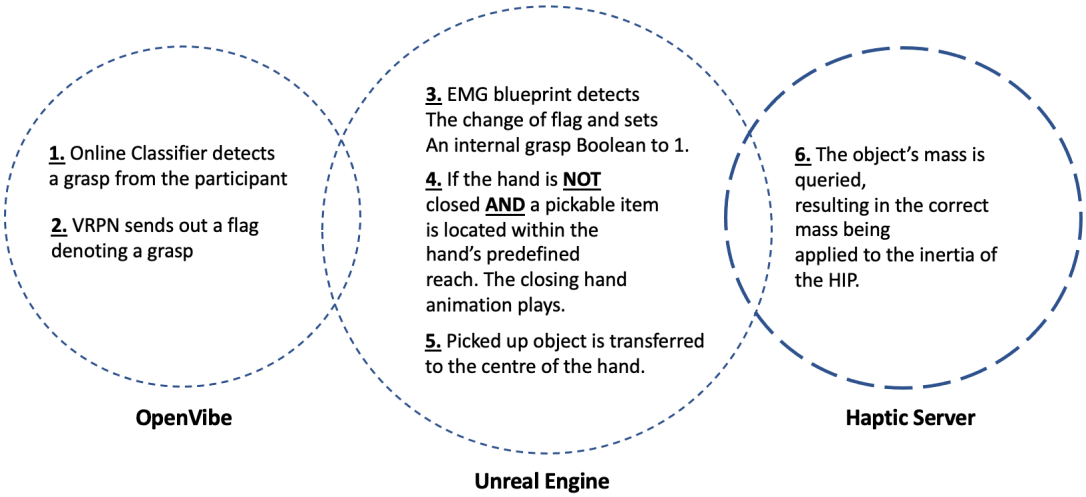


Figure 7.21: Loop flow diagram overview showing the interaction of sub systems during a grasp with the darker loop denoting the fast loop and light loops denoting slower loops.

In Figure 7.21 the starting point at OpenVibe detects that the participant has made a grasp with the residual muscles. The output of this is sent via VRPN which broadcasts the change of classifier.

During the running of the sessions a blueprint listens out for VRPN broadcasts and assigns a Boolean to that output (also saving raw data sent from OpenVibe directly to

Unreal Engine). The main blueprint that drives the avatar constantly checks for the value of this Boolean. When the grasp Boolean is set to true this starts the grasp routine.

The first part of the routine checks if the hand is not closed (set via another Boolean), if this is false the routine proceeds along to check if there is an item to be grasped. This is facilitated in two ways, first the object to be grasped has to be of a certain type of object (graspable) set in the object's properties to ensure that only certain types of objects can be picked up. Secondly a collision sphere is placed on the centre of the hand with an area slightly bigger than the hand itself. If the object is a "graspable" object and if the object is inside the collision sphere located in the palm of the hand then the closing hand animation is played and the object is "attached" to the centre of the hand to give the appearance of the hand holding an object. This also enables correct rotation when moving the hand as the object is considered a "child" of the "parent" hand attachment.

During this attachment the object's mass is queried, converted into Newtons, and sent to the Haptic Server so that the moment of inertia can be correctly applied to the end effector. The object is now "attached" and can be transported within the environment, being part of the end effector means that other interactions such as collisions can be applied to the grasped object. However if the haptics Boolean is set to false there is no change in the value of the inertia.

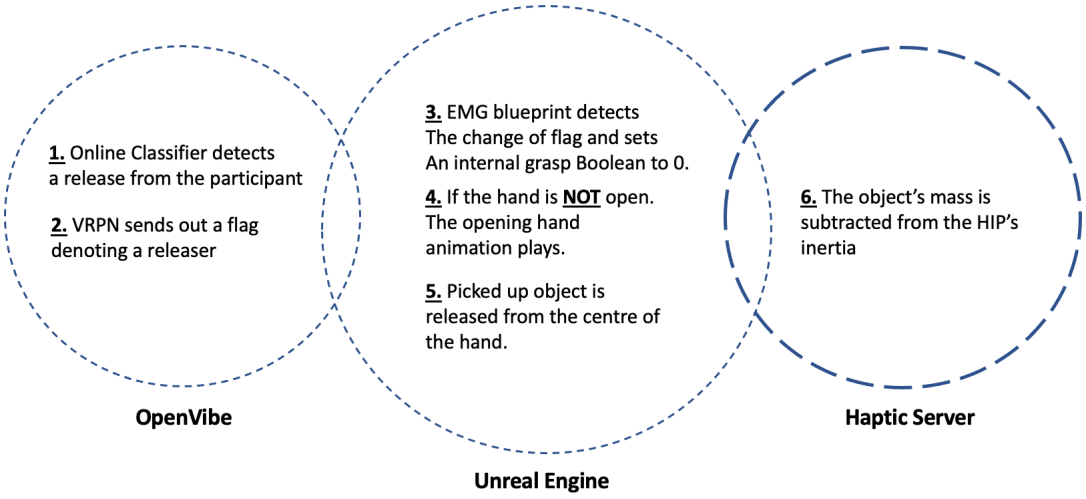


Figure 7.22: Loop flow diagram overview showing the interaction of sub systems during a release with the darker loop denoting the fast loop and light loops denoting slower loops.

When the online EMG classifier detects a releases from the residual muscles similar to the grasp; the information is passed on to Unreal Engine and if the hand is not open,

the opening hand animation plays, the object is released from the attached point and the information is sent to the Haptic Server to subtract the added inertia from the end effector.

7.6.2.2 Object Collision

The other main interaction handled by the system is that of object collisions. Again as per above no force feedback is provided if the haptics Boolean is set to false. In this flow diagram shown in Figure 7.23 only two sub systems are involved in handling object collisions; Unreal Engine and the Haptic Server. Within this interaction both the physics engine and visual engine within Unreal Engine are utilised sending data to the haptics server working together.

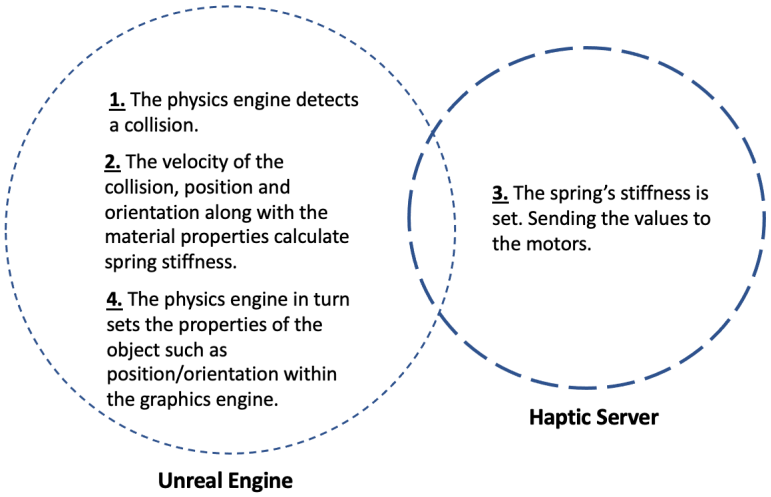


Figure 7.23: Loop flow diagram overview showing the interaction of sub systems during an object collision with the darker loop denoting the fast loop and light loops denoting slower loops.

Once a collision has been detected via the physics engine, data about this collision (position, orientation, velocity and material properties) of the objects that have collided with the GOD object are calculated and sent to the Haptic Server. At a result the Haptic Server applies the correct values to the main spring and damper values sent from Unreal Engine. As the same time this is happening within Unreal Engine the graphics engine is updated to correctly apply information from the physics engine.

7.7 Summary

This chapter has examined the core components that make up the system. The modular nature of the system is beneficial in making it straight forward to replace parts of the subsystem; from the headset to the robot.

As highlighted in the Chapter 5, previous research using virtual reality systems have identified gaps in hardware/software knowledge which this research has addressed. Mainly the use of fully immersive virtual reality using a HMD, with fully anatomically correct inverse kinematics for both limbs, along with the use of biofeedback to aid embodiment and agency with a force feedback robot to enhance embodiment.

This is mainly due to the use of Unreal Engine 4; itself designed to be modular and flexible. However due to Unreal Engine's main purpose in being aimed at game development some aspects such as integrating specialist equipment such as robotics and amplifiers for biological signals at first required complicated fixes or custom plug-ins. Due to the proliferation in uptake of Unreal Engine over the years more custom hardware and usage is now common place.

The success in implementing such a system is built on years of technology progress, with a spurt in the last decade based on the cost of components in general and also the quality of visual based components such as LCD screens for headsets and sensors for tracking external equipment. It is these advancements that has made the research possible, in combination with software tools such as Unreal Engine and modern graphics which has made the environments as life like as possible. It also allows the future of the work to potentially become more portable and lower cost, enabling potentially more uptake in health services such as the NHS and not just private funded schemes.

As highlighted by Figure 7.2 The system is based on three core elements; 'Feel, Control, See' which is not only novel in its approach but does so utilising paradigms in previous research such as mirror box therapy style virtual reality systems. Taking this idea of 'Feel, Control, See' one potential outcome could be to propose a new model to describe Phantom Limb Pain (Figure 7.24). The proposed model is in line with Makin's recent essay [126] in that it is argued that the somatosensory cortex cannot be tricked into organising simply through visual information. Therefore the combination of movement of the residual limb coupled with proprioceptive feedback enhanced through tactile stimuli as proposed in this thesis, might merit cortical reorganisation and preservation of the missing limb. Erlenwein et al [124] further advocates that current mechanisms of cortical reorganisation should not be considered in isolation but instead complementary to each other. However, the model proposed in Figure 7.24 would need to be validated through neuroimaging studies which

is out of scope of the thesis presented herein.

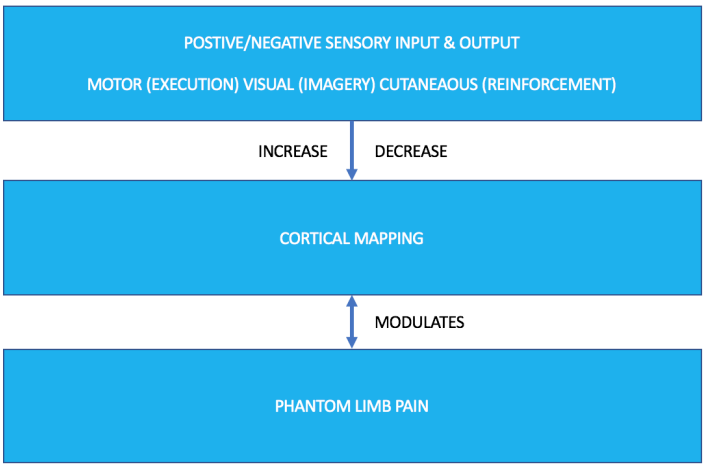


Figure 7.24: Proposed model for Phantom Limb Pain focusing on Motor (Execution) Visual (Imagery) and Cutaneous (Reinforcement) areas

What follows in the next chapter is the methodology for the feasibility clinical study in order to test the hypothesis laid out in chapter one.

Chapter 8

Feasibility Clinical Study

8.1 Introduction

Previous work on using virtual reality in order to alleviate Phantom Limb Pain has had some success as shown in Chapter 5. These studies have focused on virtual only approaches in order to facilitate embodiment of a virtual limb and EMG or trackers to map the affected limb into a virtual space. The conclusions of this initial work has highlighted the addition of stimuli such as tactile feedback in order to increase embodiment to help alleviate Phantom Limb Pain. The system described in Chapter 7 includes this missing element, with this chapter providing first the methodology of the feasibility clinical study including measures and study design after which the results will be discussed from section 8.4 onwards. It draws on research discussed in chapter 4 regarding pain post amputation, and approaches detailed in chapter 5 in terms of treatment options and 6 looking at embodiment and agency.

8.2 Clinical Study Design

Presented in this Chapter is the feasibility clinical study using the system created and discussed in Chapter 7 on a population of upper limb amputees suffering from Phantom Limb Pain. The study was reviewed by the Dstl, Ministry of Defence and NHS ethics committees, raising no objections on ethical grounds and allowed the project to proceed. In addition the project was included on the NIHR portfolio (IRAS Project ID: 179870 ; REC Reference: 15/WM/0147). Additional ethics documents related to the study can be found in Appendix F.1, both the participant information sheet (PIS) F.1.1 and the consent form F.12. The protocol sent for NHS ethics can be found in Appendix B. The project examined the following objectives:

8.2.1 Objectives

1. To develop an immersive virtual reality and haptic robotic system that allows upper limb amputees to take part in exercises that involve:
   (a) movement of the affected limb tracked by the robot;
   (b) classified muscle activity from the affected limb to open and close a virtual hand that would allow reach, grasp, transport and release of objects;
   (c) provide force feedback when manipulating objects in the virtual environment (e.g. feel object physical properties such as geometry, weight, friction, collisions) to mimic real physical interactions.
2. Carry out a feasibility clinical study with a cohort of upper limb amputees who are clinically diagnosed with Phantom Limb Pain to examine the feasibility of its use in a clinical setting and its effect on pain.

8.2.2 Materials and Methods

The system was located at two centres during the feasibility clinical study, the Royal National Orthopaedic Hospital (RNOH) at Stanmore and the West Midlands Rehabilitation Centre, Birmingham (BCHC). The RNOH was the main centre with BCHC contacting the RNOH expressing an interest in being part of the study as it was on the NHS portfolio for clinical studies. As a result additional centres could be part of the feasibility clinical study, the West Midlands Rehabilitation Centre had previous links to the RNOH hence the additional participants from BCHC.

Participants were assigned to either the VR + Haptics group (visual surrogate for the missing limb with haptic feedback) or VR group (visual surrogate for the missing limb without the haptic feedback). As the study is a feasibility clinical study both transradial and transhumeral amputees regardless of their time since amputation and prosthesis use were included in order to inform future more focused studies.

To balance the groups participants during the baseline session were graded on a seven point scale (very poor to very good or −−− to +++ shown in Table 8.1) by the experimenter and clinical colleagues on both the range of motion and EMG quality. This was used in conjunction with other factors such as gender, age, time since amputation, prognosis, amputation

side and level, prosthesis used, onset of Phantom Limb Pain and medication. Due to the stratified population balancing the groups did lead to an unbalanced population within groups.

The experimenter did not have any contact with the participants until the consent session. Communication between the participants and hospital was achieved via the Research & Innovation Centre (RIC) at the RNOH, participants were drawn from patient lists within the hospital.

Participants were free to withdraw from participation in the study at any time on request.

The reported pain levels were monitored every session and reported to a qualified therapist, who alone without the experimenter's input decided on the need to follow it up with the participant and if need be advise on withdrawing from the study.

The withdrawal criteria was based on standard clinical studies for pain related participants, and although potential bias in terms of withdrawing participants due to sustained extreme pain spikes could not be fully eliminated no participants who were consented to the study withdrew.

Some studies reported in the literature have shown, along with the preliminary results of the study:

- long-term prosthesis user could experience less vivid phantom limb sensations, however the pain persisted [213].
- Non-traumatic amputees still experience phantom limb sensations and residual/stump pain, however this is less severe than traumatic amputees [39]. In terms of sensation and phantom hand representation this does seem to be true, however in terms of pain the results of the study are inconclusive.
- Phantom Limb Pain regardless of the site of amputation leads to the same acute and chronic pain suffered by all patients [103]. All participants in the study stated that they experience a "background" pain which can be considered chronic with regular spikes of pain which has been attributed as acute pain, leading to similarities between the participants.

8.2.3 Case Studies

Twelve participants completed the study using the protocol outlined in the previous section. Due to the low number of participants and stratified population not providing enough

statistical power to allow a comparison of pain and embodiment results between the two groups (as discussed in section 8.4.1), the analysis carried out in section 8.4.2 presents the results as single case studies.

Participants selected by clinical professionals in order to take part in the study had to fulfil the criteria in the following two sections.

8.2.3.1 Inclusion Criteria

- Phantom Limb Pain must be present.
- Participants with a stable biomechanical situation.
- Participants aged minimum 18 years old at onset amputation.
- All upper limb amputations.
- Above the elbow amputations might require participants to wear their prosthetic limb during the intervention.

8.2.3.2 Exclusion Criteria

- Participants outside the minimum age.
- Participants that do not adequately understand verbal explanations or written information given in English (or are not accompanied by an interpreter). In case of doubt on the participant's competency to consent, the investigator will seek advice from their GP/ rehabilitation consultant before proceeding.
- Participants whose residual limb and muscle activity cannot be used with the haptic device.
- Other medical reasons that participants are unsuitable to take part.

8.2.4 Participants

An overview of the participants who took part in the study can be found in Table 8.1, with information such as age, level of amputation, side of amputation, time since amputation, if the participant wore a prosthesis, if the participant was on medication, onset of Phantom Limb Pain, baseline pain scores, which group they were assigned too with additional information on their range of motion and EMG activity. With a mean age of 45.5 years old (STD 15.2 years) and mean time since amputation being 14.1 years (STD 13.9 years). Participants were also asked during the administration of the initial McGill pain

questionnaire regarding any medication they are taking. This includes prescription or ad-hoc medication such as non prescription pain medication (paracetamol e.g). Provided in the next 12 sections is an overview of each case study. Participants recruited to the study were 50/50 transradial and transhumeral amputees, with just under half (5 out of 12) wearing a prosthesis. For transhumeral amputees to take part they were required to wear a prosthetic limb. This was necessary to maintain the kinematic chain and resolve the inverse kinematics in the virtual environment. For the transradial participants, the forces were transmitted directly through the robot attachment to the residual limb. In the case of transhumeral participants, the robot was attached to the prosthesis (through the distal limb segment) with forces transmitted through the prosthesis onto the limb. Although some variability between proximal and distal limb segments could exist, this was minimised by placing the residual limb/ prosthesis at the same physical location (e.g., forearm segment between wrist and elbow joint). The force feedback was delivered to enhance proprioception during reach to grasp movements rather than tactile sensation through texture perception. ăIn addition, 5 of the participants had brachial plexus injuries as well as their amputation.

Participant ID	Age	Amputation Side	Amputation Level	Time since Amputation (Years)	Prosthesis Used	Onset PLP	Medication	Baseline Pain Score	ROM	EMG	Group
P01	58	Right	Transhumeral	30	Cosmetic	Since operation	Yes	2	--	--	VR
P02	26	Right	Transhumeral	1	Cosmetic	6-7 months post operation	No	4	+	+++	VR & Haptics
P03	67	Left	Transhumeral	6	None	Since operation	Yes	2.5	-	+	VR & Haptics
P04	35	Left	Transhumeral	1	None	Since operation	Yes	2	-	+	VR
P05	26	Left	Transradial	1.5	Cosmetic	Since operation	Yes	5	+	+	VR & Haptics
P06	49	Right	Transradial	8	Cosmetic	Since operation	Yes	5	+++	++	VR
P07	76	Left	Transradial	42	Cosmetic	3 weeks post operation	Yes	3	---	-	VR
P08	52	Left	Transradial	2	None	Since operation	Yes	3	+++	+++	VR
P09	46	Right	Transradial	2	None	Since operation	No	4	+++	++	VR & Haptics
P10	43	Left	Transhumeral	26	Cosmetic	Since operation	Yes	2	--	+	VR
P11	38	Left	Transhumeral	1	Cosmetic	Since operation	YES	4.5	+++	++	VR & Haptics
P12	30	Right	Transhumeral	14	Cosmetic	Since operation	No	2	+	++	VR & Haptics

Table 8.1: Table showing general participant information. Including grading of ROM and EMG detailed in Materials and Methods (Very poor to very good or −−− to +++)

8.2.4.1 P01

Participant P01 had their amputation 30 years prior due to a traffic accident whilst on a motorbike. The initial accident caused a brachial plexus lesion and as a result an amputation was carried out. A right sided transhumeral amputee who did use a prosthesis since being

fitted post amputation. The participant did take a range of medication however found the prescription to be inadequate in controlling the pain stating "no effect (in terms of pain relief), just makes me sleepy" scoring the effectiveness of the medication as a 1 out of 5 (1 being very ineffective to 5 being very effective) during the preparation session. The participant stated in the preparation session that the pain felt like "white noise" around the elbow joint as a buzzing, constant pain with occasional spikes and general feeling of a pins and needles the that area. P01's stated that their sleep was reasonable which was not particularly affected by the pain.

8.2.4.2 P02

Participant P02 was involved in a traffic accident while on a motor bike in September of 2015 with an amputation shortly afterwards. Initially post accident P02 experienced no pain however in May 2016 the participant started to experience Phantom Limb Pain, in addition P02 suffered a partial brachial plexus lesion. A transhumeral level amputee who since being provided with a prosthesis post amputation constantly wore it due to their job. Despite the high levels of pain reported during the preparation session (4 out of 5 on the McGill Questionnaire) the participant did not take any medication at the time of the study, having previously been prescribed Gabapentin. Sleep was also affected which had a knock on effect on their mood which caused pain spikes. P02 used distraction to take their mind off the pain, using video games in a first person perspective as often arms are present on the screen. Previously P02 had used traditional mirror box therapy twice per day but found that it had no effect on pain levels.

8.2.4.3 P03

Participant P03's amputation was six years prior to taking part in the study due to a traffic accident, on the left side at transhumeral level. Initially the arm was completely crushed with soft tissue beyond repair which resulted in the amputation. The participant did not use a prosthesis before the study and had to be provided with a cosmetic prosthesis to take part in the study due to their level of amputation. P03 did state that they "don't know how to live without pain medication", with pain levels generally around 2.5 out of 5 (McGill Questionnaire) before the study and intermittent spikes to 4 out of 5. With respect to pain spikes P03 during the preparation session stated that initially pain medication did help

shortly after the amputation but not so much "now". Pain sensations of cramp, burning, pins and needles were experienced by P03 located on the phantom hand even experiencing pain "when touching objects with their stump". Within P03's phantom hand they could feel all 4 fingers and their thumb, although with limited control.

8.2.4.4 P04

Participant P04 was a transhumeral amputee via a traffic accident who suffered additional injuries including a brachial plexus injury. As a result of their injuries P04 elected to have an amputation. Similar to P03, P04 did not use a prosthesis day to day so had to be supplied with a cosmetic prosthesis during the intervention sessions. The participant had been on a number of prescribed pain medication since the accident which they had found "somewhat helpful with the pain", however the side effects were having an impact on their day to day life. The participant's sleep was severely effected, finding it hard to fall asleep, waking up all the time and experiencing bad dreams which lead to pain spikes and issues with mood also effecting pain levels. Similar to P03 the participant did not engage with the prosthesis outside the intervention sessions. P04 stated that "(they) see pain as a normal feeling now" with pain levels generally around 2 out of 5 (McGill Questionnaire) with spikes up to 5. Pain sensations consisted of electrical shock/bursting pain within the missing limb in addition to both freezing and heat pains all the time located in the missing limb.

8.2.4.5 P05

Participant P05 experienced a motorbike injury which resulted in a brachial plexus lesion who subsequently underwent transradial amputation a year and a half before taking part in the study. P05 was a prosthesis user (cosmetic) since their amputation and was heavily engaging in using it as part of their job. P05 was taking medication for their Phantom Limb Pain since amputation who rated its effectiveness as 3 out of 5. P05's pain began since the accident and "hadn't really changed, perhaps got used to it", with a pain score at the preparation session of 5 out of 5. P05 stated that their pain felt like a crushing sensation located in their missing limb down to their hand, with said pain feeling like a "fizzing pain building up to said crushing pain (as the pain spikes) leading back to the fizzing pain". In addition the crushing pain lasts between 5-10 seconds or more if P05 "fights the pain". P05 stated that their phantom hand feels broken apart, with most pain in the little finger, ring finger and along the phantom limb

to the stump. In addition different parts of the phantom hand such as fingers feel as if they are located within different parts of their stump and phantom hand, and that they are static as they "stay in the same position". P05 had previously used traditional mirror box therapy with no effect on their pain levels, however as stated there was "no negative effect either".

8.2.4.6 P06

Participant P06 suffered an amputation due to a traffic accident nine years prior to taking part in the study, initially experiencing a brachial plexus lesion who elected to have an amputation at transraidal level. The participant did not wear a prosthesis day to day despite being provided with one since amputation, whilst also being on medication for the Phantom Limb Pain. The participant stated that they "did not find the medication effective for treating my pain" scoring 2.5 out of 5 for effectiveness. During the preparation session P06 stated that their pain level scored 5 out of 5, which consisted of a cold crushing pain on their fingers of their phantom hand. In addition that their fingers feel broken and that they shouldn't be moving them and has no control of their phantom hand, however that moving arm there is some pain relief. P06 had previously used traditional mirror box therapy straight after their accident but found it did not help with pain relief, however years after the accident trying it again had limited but short lasting pain relief.

8.2.4.7 P07

Participant P07 was a long term amputee as a result of a traffic accident 50 years prior to starting the study, who initially had a brachial plexus lesion and elected 8 years post accident to have a transradial amputation. This was due to issues with blood circulation and pain, which started 2 to 3 weeks after the accident. P07 did not wear a prosthesis day to day despite being provided with one after the amputation. P07 stated that their phantom hand was located around their elbow, just within the stump and also that they experienced sensations on the stump. Previously P07 had no experience of mirror box therapy, and that they had not been on medication for their pain as they found it very ineffective for relief.

8.2.4.8 P08

Participant P08 after an accident which lead to nerve damage elected 2 years later to have an amputation at transradial level on their left side. A regular prosthesis wearer post amputation

however stated that (the prosthesis) "became a hindrance" and was looking at attending an appointment post study to get the prosthesis and stump reexamined. P08 stated that they were in constant Phantom Limb Pain between the levels of 3 and 5 out of 5, finding that if they held their stump during pain spikes it had some but limited effect on pain. Despite high levels of pain P08 did state that they found the medication effective at treating their pain scoring 4 our of 5 for effectiveness. Sleep was also affected for P08 who often woke up 2 to 3 times a night with shooting/electrical shock type pains in their phantom limb. P08 did state that they could control the phantom hand and could feel said hand, with one strategy they found when pain spikes occur being to contract their muscles which controlled their phantom hand. In addition P08 had experienced traditional mirror box therapy for 6 months post amputation, however found it to have no affect on pain levels.

8.2.4.9 P09

Participant P09 a transradial amputee, who elected to have an amputation after suffering an injury to a finger which resulted in Complex Regional Pain Syndrome (CRPS) that lead to a deformed limb and a resulting elective amputation of the arm. The participant did not wear a prosthesis due to the painful sensation at the proximal end of the stump, however the participant could clearly describe both the Phantom Limb Pain and CRPS pain. Despite the high levels of pain, the participant did not take any medication for either pain sensations as it made them drowsy/sleeping and they felt none of the prescribed medication had an affect. Sensations P09 experienced included the feeling of their stump being crushed, which started straight after the amputation. P09 could control their phantom hand however "it felt stiff when doing so" and had previously experienced traditional mirror box therapy but with no affect on pain levels. In addition P09 had a spinal cord stimulator fitted to help alleviate the pain but the stimulator failed to work.

8.2.4.10 P10

Participant P10 a transhumeral amputee due to a traffic accident who suffered a brachial plexus lesion and underwent an elective amputation. P10 did not wear a prosthesis but was on medication for Phantom Limb Pain which the participant did not find effective scoring a 1 out of 5 for effectiveness. The participant was a long term amputee whose pain level on baseline taken at the preparation session was 2 out of 5, and who stated that they felt

the pain changes with the weather. Sensation wise P10 experienced pain on the back of the thumb within the phantom hand with pain shooting to the elbow and then to their shoulder resulting in severe pain spikes. P10 stated they could mentally picture opening and closing their phantom hand and at the same time perform a pinch grip with their hand, however their muscles on their stump as a result get stiff in which P10 stated that massaging helps and that tiredness seems to cause an increase in pain.

8.2.4.11 P11

Participant P11 a transhumeral amputee as a result of a traffic accident a year prior to the study elected to have an amputation due to nerve damage, muscle failure and blood clots within the affected arm. P11 was on medication since the accident however found the medication to be very ineffective in treating their pain, but was provided with a cosmetic prosthesis which they used. Pain sensations were mainly located on palm and thumb of the phantom hand were noted by P11 as being "severe, feeling like pins and needles" scoring 4 out of 5 baseline pain during the preparation session also noting that there was no sensation of any forearm either. P11's Phantom hand was stationary in position but could rotate hand needing to concentrate alot to do so, with the phantom hand located on the stump with no control in terms of opening or closing the hand, also experiencing hot and cold sensations. On the stump P11 stated that they have good sensation and can feel different temperatures on the stump such as warm water during showering despite nerve damage.

8.2.4.12 P12

Participant P12 experienced a brachial plexus lesion as a result of a traffic accident and elected to have a transradial amputation 14 years prior to taking part in the study. Despite being a long term amputee, the participant was only a prosthesis user for a short time before the study started. Despite being on medication for 2 years post amputation P12 stopped the prescription due to finding it very ineffective and pain being considered "mild" at around 2 out of 5 stated at the preparation session. Sleep was heavily affected for P12 three times every week, which also affected their mood. Pain sensations were generally located at the stump but at times within the phantom hand feeling like pins and needles and pulsing spikes, in which the phantom hand was located on their elbow in a clinching position having simple open/close control of said hand.

8.2.5 Procedure

A summary of the study timeline is shown in Figure 8.1 with a detailed plan of the study in Table 8.2 showing in addition to the session name the activity associated with that session and the duration of each session. Each session type will now be broken down and explained below in detail.

Figure 8.1: Study Timeline

8.2.5.1 Initial Meeting

Participants who had been contacted via the Research Innovation Centre (RIC) at RNOH or via clinicians at the West Midlands Rehabilitation Centre were invited to an initial meeting in which the participant information sheet (located in Appendix F.1.1) was provided if not already, the study was further explained, any questions answered and consent was taken (located in Appendix F.1.2). During the initial meeting the member of the RIC or clinician was also present.

8.2.5.2 Preparation Session

The initial meeting was followed later by a preparation session used to set up the sensors, examine the range of movement and conduct EMG pattern recognition for each participant. This enabled participants to be grouped as well as add additional software alterations to be performed in order for the participant to take part in the study (e.g scaling of movement due to ROM limitations). Participants were not told which group they were assigned and no discussions took place that described the differences between the groups. An initial McGill pain questionnaire (located in Appendix B) along with a short interview was also taken in order to assess a baseline pain score, medical history along with allocation of a pain diary. Participants are asked to record any reflections on their pain, mood, sleep and ad hoc information they wish to write down from the preparation session to the final Follow Up session.

8.2.5.3 Intervention Sessions

The subsequent three weeks involved nine sessions (60 minutes on the VR and Haptics system) spread evenly. This duration was chosen due to previous studies based on intensive robotic intervention and studies on stroke therapy [208][214]. Previous studies on Phantom Limb Pain and VR therapy range greatly from a single session, one session per week or month for a set number of months as there is no clinically validated period as most studies including the one presented in this thesis are feasibility studies. However further results reported in the literature shows that an intense exposure to robot therapy is often necessary to observe significant cortical reorganisation with the damaged brain and improved kinematic features (e.g. limb synergies and task oriented movements). Therefore three weeks of intense therapy of three hours per week was decided as a balance between significant time on the robot and allowing periods of rest in between sessions to accommodate the schedules of the participants. The steps taken during each session are as follows:

- Brief discussion with the participant to establish how they have been since the last session.
- Setting up of sensors on the participant.
- The pre intervention proprioceptive drift measurement is taken.
- The participants amputated limb is placed in the gimbal attached to the HapticMASTER.
- The session now beings with the exercises, with short breaks when needed as denoted by the participant. This lasts one hour.
- The post intervention proprioceptive drift measurement is taken.
- Taking off sensors on the participant.
- McGill pain (short) questionnaire and Botvinick's embodiment questionnaire are taken.
- The session is over and the participant leaves.

8.2.5.4 Post Intervention

After the ninth session two follow up sessions are scheduled, Follow up 1 which is three weeks after the ninth session and Follow up 2 (the final follow up session) which is

scheduled six weeks after Follow up 1. In addition participants are asked to carry on writing in their pain diaries until the final Follow Up session. During these three weeks, no formal training is received.

8.2.5.5 Follow Up Sessions

The subsequent two follow up sessions involve an in person meeting with the participants. The McGill pain (short) questionnaire is taken (to determine pain scores since the last intervention session) along with a short interview to see how participants are doing in terms of mood, sleep and general wellbeing. This is the same for the final Follow Up session in addition to the pain diary being collected, after which the participant has completed the protocol.

Session	Activity	Duration
Initial meeting	• Explain the purpose of the study and answer any questions • Provide written informed consent for participation in the study	30-60 min
Preparation session	• Determine the set up of the different sensors • Establish a simple EMG pattern recognition from the participant's residual limb • Moulding a residual limb interface cuff to the haptic device for comfort and function. • Take initial Pain questionnaire • Pain diary provided for the duration of the study	60-90 min
Intervention session (3/week, 1 hour each) Weeks 1-3	• Set up sensors • Measure proprioceptive drift • Perform tasks with AMPSIM (take up to 10 min break if necessary) • Measure proprioceptive drift • Take off the sensors • Complete the embodiment and the McGill Pain questionnaire	Initial 10 min 60 min Last 10 min
Post intervention Weeks 4-12	• Participants are asked to keep a Pain diary • No formal training received	NA
Follow up session Week 6	• Take Pain questionnaire • Conduct Interview • (determine if any reduction on perceived pain levels reported during first 3 weeks post intervention is retained)	30 min
Final follow up session Week 12	• Take final Pain questionnaire • Collect pain diary from participant • (determine if any reduction on perceived pain levels reported during the pilot study is retained at the end of 12 weeks)	30 min

Table 8.2: Detailed Study Timeline. Showing Initial consent meeting, preparation sessions in which baseline pain measures were taken, three weeks of intervention sessions totalling nine hours, three weeks of no intervention, leading to two follow up sessions

8.3 Feasibility Clinical Study Outcome Measures

8.3.1 Clinical Assessment Measures Used

8.3.1.1 McGill pain (short) questionnaire

Used to measure perceived levels of pain experienced by the participant taken at the beginning of the study, at the end of each therapy session and at a follow up session. The traditional version was developed by Melzack and Torgerson in 1971 [215] with the short form version used in this study in 1987 [216]. The short version was created in response to the lengthy time it took to administrate the original version.

The short McGill pain questionnaire (SF-MPQ) is broken into 4 sections, 2 qualitative sections first followed by 2 quantitative sections. It has been used in clinical practice for measuring perceived levels of pain since it's publication it is reliably validated [217]. At the time of the ethics application and running of the feasibility clinical study the McGill pain questionnaire was the standardised pain questionnaire clinically used and approved by the NHS ethics committee. In addition the original version (SF-MPQ) was preferred by our clinical collaborators as it provides information such as location of the pain and also the pattern of the pain.

The McGill pain questionnaire is located in appendix B.

Additional pain measures have been put forward such as a chronic pain measure form from Kikkert and colleagues [121] in 2017. The form focuses on asking questions based purely chronic pain neglecting acute pain also experienced by the participants. However the work by Kikkert and colleagues also strengthens the work presented in this thesis, moving away from imaginary phantom hand movements and focusing on actual phantom hand movements using the combination of robotic therapy and activation of residual muscles to control opening and closing of a virtual hand using EMG electrodes. As quoted in the above paper "While these therapies (e.g. mirror therapy and graded motor imagery) are based on the assumption that increased motor control over the phantom hand can cause a change in PLP, many of these therapies make use of motor imagery, rather than motor execution"[121]. This motor execution through robotic facilitated movement is the main focus of the work carried out in this thesis.

8.3.1.2 Botvinick's embodiment questionnaire

The embodiment questionnaire used was adapted from the original developed by Botvinick et al [183] in 1998. The purpose of the questionnaire is to gauge qualitative embodiment levels post intervention initially after the rubber hand illusion first described by Botvinick[183]. Since the original Botvinick questionnaire, studies have based their embodiment questionnaire's on this version substituting questions relevant to their study.

The questionnaire includes nine statements with participants indicating their response on a seven-step visual-analogue scale ranging from 'disagree strongly' to 'agree strongly'. The questionnaire is presented at the end of the intervention session, with participants answering based on their experience from that session.

The embodiment questionnaire protocol can be found in appendix B.

8.3.1.3 Proprioceptive drift estimation

The Proprioceptive drift estimation was used to measure the perceived level of embodiment before and after the intervention session, this measure consists of measuring the distance the participant perceives their limb has moved.

At the beginning of the session the participant sits at the table where the robotic intervention takes place with their arm/s placed on the table, whilst wearing the HMD switched off to blindfold the participant. The experimenter measures the length of the participant's intact arm or prothesis to the centre of the hand, marking this point on the amputated side with a pen/marker on the surface of the table. Once this has been done the experimenter instructs the participant using their intact hand to point were they believe their amputated hand is located, this position is also marked on the table in which both marks are measured in both the length and width sides of the table before being recorded and the participant is free to take off the switched off HMD. This process is repeated at the very end of the session after an hour on the robot.

The difference of these points are calculated and then used as the measure of proprioceptive drift.

8.3.1.4 Pain diary

Participants were asked to keep a pain diary for the length of the study until final follow up. This was used to gauge pain levels pre and post intervention up until the final follow up session using the numerical pain levels used in the short McGill pain questionnaire. Participants were encouraged to denote perceived levels of pain and to note any changes in behaviour of the phantom limb, quality of sleep and other such changes. Pain diaries have been a common secondary measure related to pain studies [218][219][220] due to the pain diaries ability to capture pain measures during studies in addition to the selected pain capture points (e.g at the end of each session). The diaries provide information that could potentially be used to shape future studies as well as complimenting participant comments on mood, sleep quality etc pre and post the intervention. The main issue with pain diaries as suggested by Stone and colleagues [221] is that patient compliance in fully completing paper pain dairies, suggesting that electronic versions provide better compliance. This is reflected in the study presented in the thesis in that the majority of the participants did not fully complete their pain diary. Future work will consider a hybrid approach looking into pre-existing online clinically validated pain dairies.

8.4 Feasibility Clinical Study Analysis and Results

8.4.1 Statistical Overview

In order to gauge if there is any statistically significant differences between the two groups a Mann-Whitney U test was run from baseline to Session 9 (During sessions) with collected output shown in Figure 8.2 and baseline to final follow up session (Overall) with collected output shown in Figure 8.3.

Distributions of the pain scores for the two groups (Group V - virtual only without haptics (force feedback, weight, texture), Group VH - virtual with haptics (force feedback, weight, texture) were not similar on baseline, as assessed by visual inspection. Pain scores during sessions for Group V (mean rank = 5.17) and Group VH (mean rank = 7.85) were not statistically significantly different, U = 26, z = 1.304, p = .240, using an exact sampling distribution for U. Indicating that the distributions of the pain scores between the two groups were different.

For the overall pain scores between the two groups, Group V (mean rank = 5.0) and Group VH (mean rank = 8.0) were not statistically significantly different, U = 27, z = 1.457, p = .180, using an exact sampling distribution for U.

Baseline pain scores were not normally distributed for Group V with a skewness of -2.227 (standard error = 0.845) and kurtosis of 2.180 (standard error = 1.741) and for Group VH with a skewness of -1.013 (standard error = 0.845) and kurtosis of -0.275 (standard error = 1.741). The Shapiro-Wilk's test was also used to confirm this due to the low number of participants, showing that the baseline pain scores were not normally distributed for both groups ($p < .05$).

Shown in Figure 8.4 is the general overview of the average McGill pain scores between the two groups, group V is coloured in blue and group VH in orange. Regardless of the group a reduction in perceived levels of pain can be seen from baseline to Session 9. Despite a slight rise on session 4 then a dip in pain levels in group V there is a clear difference in scores at the final follow up session between the groups, with group VH seeing a decrease in pain levels during the follow up sessions. Both groups show a spike in pain at the beginning of the new week (2 and 3, Sessions 4 and 7 respectively) after the weekend.

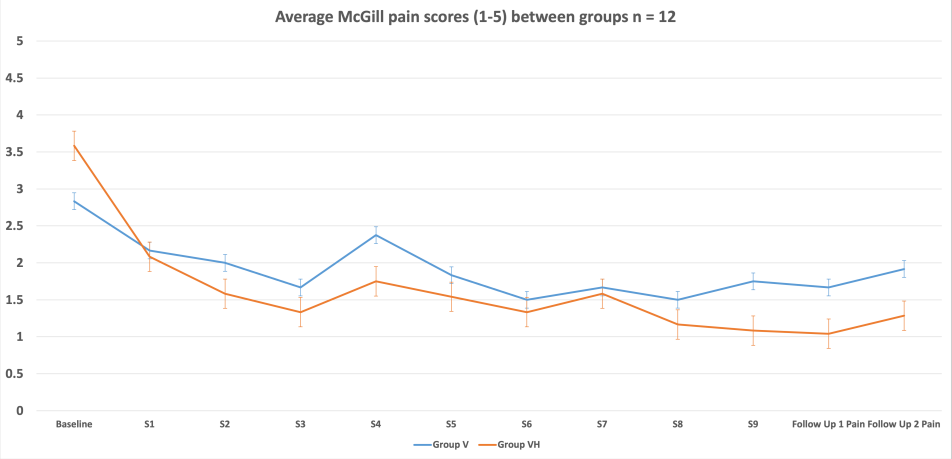
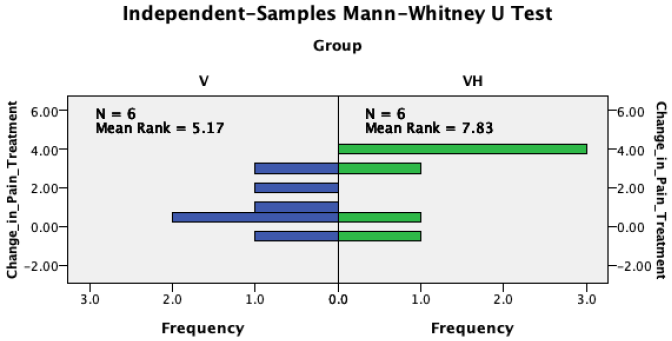


Figure 8.4: Average pain between groups from baseline session to follow up 2 session showing 12 participants, with error bars showing STD

A general percentage overview of the pain levels in terms of change from baseline to final follow up session can be seen in Figure 8.5 and during sessions (baseline to Session 9) in Figure 8.6.

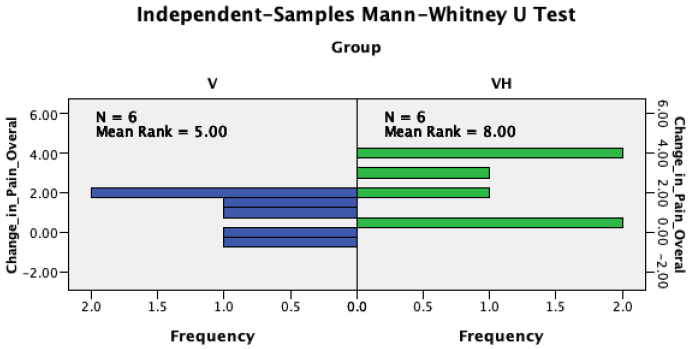
Table 8.3 shows the summarised results which will be discussed in the Chapter summary (section 8.5).

The overall percentage change regardless of the group for all participants is a mean



Total N	12
Mann-Whitney U	26.000
Wilcoxon W	47.000
Test Statistic	26.000
Standard Error	6.135
Standardized Test Statistic	1.304
Asymptotic Sig. (2-sided test)	.192
Exact Sig. (2-sided test)	.240

Figure 8.2: Output showing the results from the Independent Samples Mann-Whitney U test of the change in pain



Total N	12
Mann-Whitney U	27.000
Wilcoxon W	48.000
Test Statistic	27.000
Standard Error	6.179
Standardized Test Statistic	1.457
Asymptotic Sig. (2-sided test)	.145
Exact Sig. (2-sided test)	.180

Figure 8.3: Output showing the results from the Independent Samples Mann-Whitney U test of the change in pain overall between the two groups.

	Session %	Session	Overall %	Overall
All	56% (38%)	1.8 (1.8)	49% (39%)	1.6 (1.5)
Group V	44% (43%)	1.1 (1.2)	32% (42%)	0.9 (1.0)
Group VH	66% (38%)	2.5 (2.0)	64% (33%)	2.3 (1.6)

Table 8.3: Table showing the average percent pain decreases, along with McGill score changes. Broken into sessions (Baseline to S9) and overall (Baseline - FU2), with the bracketed values showing the standard deviation

decrease of 49% (STD 39%) in percentage and 1.6 (STD 1.5) in McGill Score, a mean decrease of 32% (STD 42%) in percent 0.9 (STD 1) in McGill Score for group V and mean 64% (STD 33%) in percent 2.3 (STD 1.6) in McGill Score for group VH.

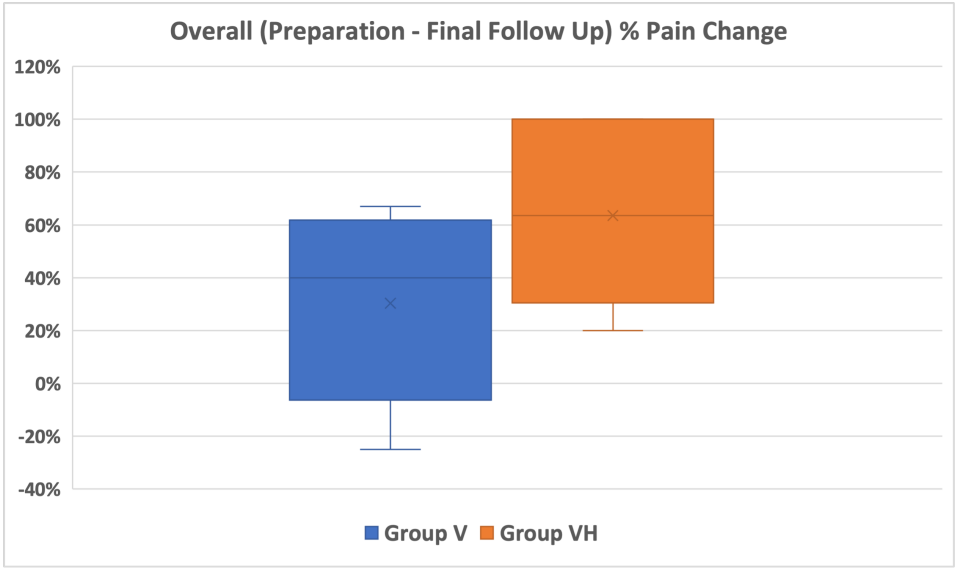


Figure 8.5: Box plot showing mean change of pain scores (as percentages) between the two groups from preparation session to follow up 2 session, with whiskers showing minimum and maximum values.

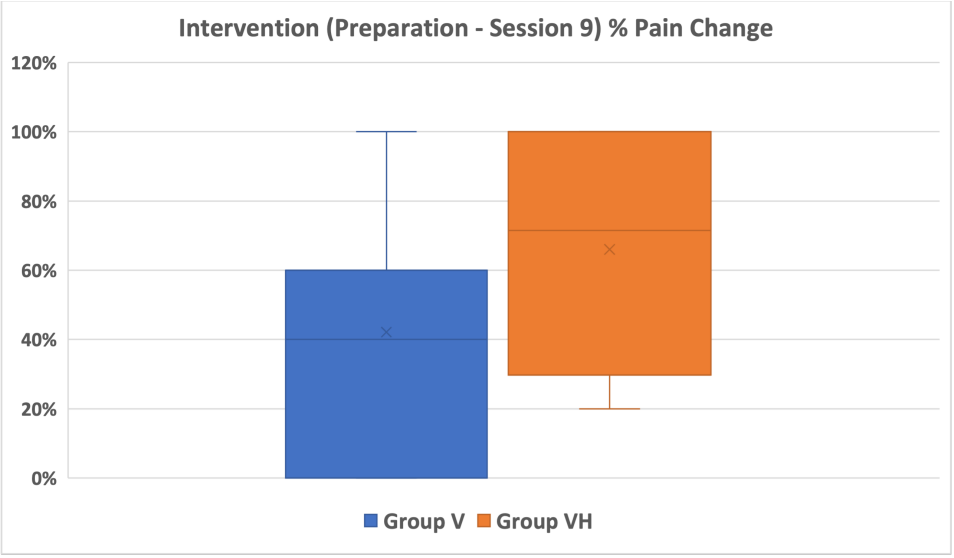


Figure 8.6: Box plot showing mean change of pain scores (as percentages) between the two groups from preparation session to session 9, with whiskers showing minimum and maximum values.

During the sessions there were no cases of increased levels of pain overall and only 2 cases of no change (baseline to Session 9, not including temporal changes) for P01 and P04.

8.4.1.1 Pain

A one way repeated measures ANOVA was used to look at statistical significances between the 3 time periods (baseline, end of intervention and end of the study), which can be seen visually in Figure 8.7. Data are mean ± standard deviation, unless otherwise stated.

Mauchly's test of sphericity indicated that the assumption of sphericity had been violated, $\chi^2(2) = 7.314, p = .026$, meaning the condition where the variances of the differences between all possible pairs of within-subject conditions were not equal leading to uneven groups.

The intervention elicited statistically significant changes in pain scores over time (Baseline/S9 and FU2 sessions), F(1.317, 14.485) = 12.038, p < .002.

Pain levels decreased from 3.20 ± 1.23 at baseline to 1.41 ±1.12 at the end of the intervention (S9), a statistically significant decrease of 1.792 (95% CI, 0.37 to 3.217) pain score, p < .014. This suggests that overall the pain reduction at session 9 compared to the baseline measurement score taken at the preparation session was statistically significant. However despite an increase in pain levels from 1.41 ± 1.12 at the end of the intervention (S9) to 1.58 ± 1.18 at the end of the final follow up session (FU2), this was not a statistically significant increase at 0.167 (95% CI, 0.82 to 0.5) pain score, p < 1.0.

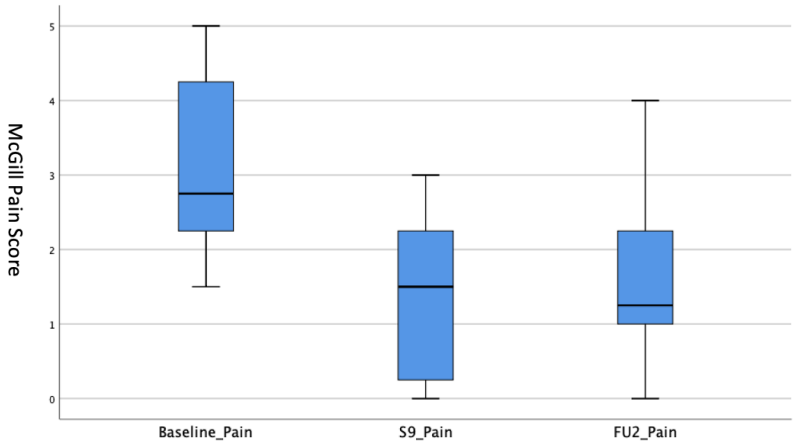


Figure 8.7: Box plot showing mean change of pain for all 12 participants regardless of group from baseline, session 9 (end of intervention) and final follow up session (FU2), with whiskers showing minimum and maximum values.

From a purely pain perspective the intervention (spanning both groups) has shown its capability in reducing Phantom Limb Pain, with no side effects being reported unlike pharmacological solutions described in section 5.2.2.

The next section will examine the embodiment and the proprioceptive drift results.

8.4.1.2 Embodiment

The two measures for embodiment captured were 1) the embodiment questionnaire [183] and 2) proprioceptive drift, as detailed previously in this Chapter (section 8.3.1), with the questionnaire data being analysed first here in this section.

8.4.1.3 Embodiment Questionnaire

The embodiment questionnaire detailed previously in this section 8.3.1, features 9 questions providing 7 possible answers.

The results presented in this section will focus on questions 3 and 7 "I felt as if the virtual limb were my (real) limb" and "It felt as if my (real) limb were the virtual limb.". This is due to the generalised nature of these two questions along with the similarities between them (e.g. asking if they belived the virtual limb were their real limb and if their real limb were the virtual limb), other questions in the questionnaire are more focused on finer details of embodiment.

The mean scores for both question 3 and 7 are plotted as a boxplot in Figures 8.8 and 8.9, the plots show the first, mid and last intervention session due to the fact that the embodiment

questionnaires were only asked during the intervention sessions.

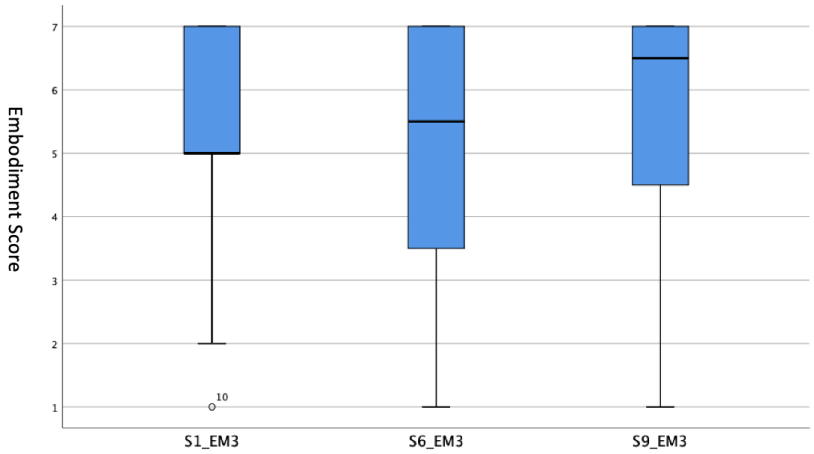


Figure 8.8: Box plot showing mean scores from question 3 of the embodiment questionnaire from 3 sessions with question 7 being displayed below; S1 the first session, S6 around the middle of the intervention and S9 the final session, with whiskers showing minimum and maximum values.

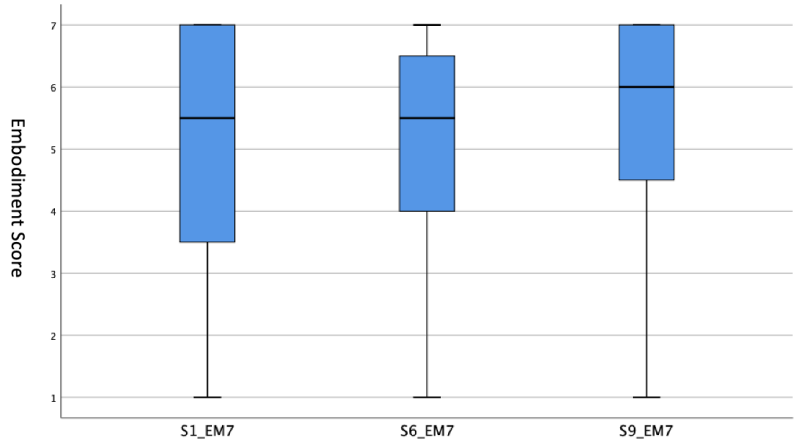


Figure 8.9: Box plot showing mean scores from question 7 of the embodiment questionnaire from 7 sessions; S1 the first session, S6 around the middle of the intervention and S9 the final session, with whiskers showing minimum and maximum values.

Despite low participant numbers a one way repeated measures ANOVA was used to look at statistical significances between 3 time periods during the intervention (S1 (start of intervention), S6 (roughly mid way) and S9 (end of intervention)) Data are mean $\pm$ standard deviation, unless otherwise stated. These three time periods were chosen due to the embodiment questionnaire being carried out during the intervention sessions, unlike the pain questionnaire which was taken also at baseline and during the follow up sessions.

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
AVG_Q7	V	6	5.6767	1.51052	.61667	4.0915	7.2619	3.66	7.00
	VH	6	4.9583	2.23840	.91382	2.6093	7.3074	1.00	7.00
	Total	12	5.3175	1.85885	.53660	4.1364	6.4986	1.00	7.00
AVG_Q3	V	6	5.2031	1.25170	.51100	3.8895	6.5166	3.66	6.67
	VH	6	4.9977	2.10805	.86061	2.7854	7.2099	1.33	6.88
	Total	12	5.1004	1.65638	.47816	4.0480	6.1528	1.33	6.88

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
AVG_Q7	Between Groups	1.548	1	1.548	.425	.529
	Within Groups	36.460	10	3.646		
	Total	38.008	11			
AVG_Q3	Between Groups	.127	1	.127	.042	.842
	Within Groups	30.053	10	3.005		
	Total	30.180	11			

Table 8.4: Single Factor Anova results between the two groups over 9 sessions mean embodiment scores for the 9 questions.

Embodiment Question 3 scores decreased from 5.16 ± 1.94 at S1 to 5.08 ± 2.23 at S6, not statistically significant. There was a slight increase in scores from 5.08 ± 2.23 at S6 to 5.5 ± 1.97 at the end of the final intervention session (S9), this again was not a statistically significant increase $p > 0.05$.

Very similar results are shown in Embodiment Question 7 scores, with no increase in mean (5.0) from S1 to S6 however a slight improvement in standard deviation from $\pm$ 2.37 to $\pm$ 1.95. There was a slight improvement from S6 5.0 ± 1.95 to S9 5.5 ± 1.83, this was not a statistically significant increase $p > 0.05$.

A single factor ANOVA was carried out for the mean embodiment scores to observe any statistical differences between the groups and can be found in Table 8.4, again highlighting the lack of statistical significance between the groups with a p-value of > 0.05.

One issue that does arise scoring embodiment levels from the embodiment questionnaire is it's use originally as a single session/instantaneous measure of embodiment as per the rubber hand illusion experiment. This does suggest that using such a format of questionnaire for longer experiments over weeks not just a single session might be called into question. Information such as the location and control of a participant's phantom hand could potentially be a better indicator of embodiment rather than a questionnaire based at the end of an intervention session.

Descriptives

Diff_Distance_X_Y_Mean

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
V	6	.50437	2.083325	.850514	-1.68195	2.69068	-2.349	3.138
VH	6	.34204	3.164330	1.291832	-2.97872	3.66280	-5.092	3.145
Total	12	.42320	2.555657	.737755	-1.20058	2.04699	-5.092	3.145

ANOVA

Diff_Distance_X_Y_Mean

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.079	1	.079	.011	.918
Within Groups	71.766	10	7.177		
Total	71.845	11			

Table 8.5: Single Factor Anova results between the two groups over 9 sessions mean distance in the x and y axis.

8.4.1.4 Proprioceptive Drift

Figure 8.10 shows the mean difference between pre and post measures for the two groups overall. Group VH does have the larger difference, 0.74 cm than group V at 0.27 cm giving a difference of 0.47 cm.

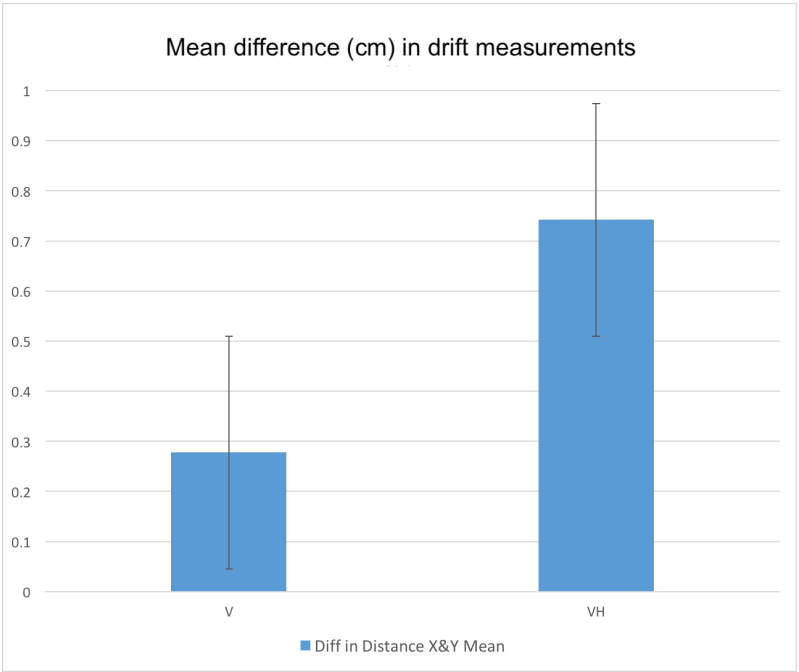


Figure 8.10: Proprioceptive drift mean values taken for the two groups (V and VH) during the 9 intervention sessions. Error bars are standard deviation.

A single factor ANOVA was carried out for the mean distance in the x and y axis with the full results found in Table 8.5. With a p-value of 0.9, no statistical significance can be drawn from the mean distance in the x and y axis.

Additional analysis of the proprioceptive drift measures can be found in appendix E.

However to summarise the results a Spearman's Correlation (due to the low participant numbers, highlighted by Aggarwal et al [222]) was carried out to observe any relationships between the embodiment questionnaire (average question 3 and average question 7) together with the average difference in distance in cm of drift experienced by the participants during the sessions. The results of this analysis can been seen below:

1. There was no statistically significant, strong negative correlation between the difference in distance in the x axis and the average question 3, r_s = -0.49, p = 0.879
2. There was no statistically significant, moderate positive correlation between the difference in distance in the x axis and the average question 7, r_s = 0.36, p = 0.912
3. There was no statistically significant, negligible correlation between the difference in distance in the x and y axis and the average question 7, r_s = 0.157, p = 0.626
4. There was no statistically significant, negligible correlation between the difference in distance in the xand y axis and the average question 3, r_s = 0.091, p = 0.778

The results of the proprioceptive drift yield little or no further clarity on embodiment. Several reasons could be behind this such as the traditionally single session set up that proprioceptive drift is used as a snapshot rather than over long time periods. However as examined in the Phantom Limb Hand(see appendix E.2), creating a measure which combines agency with the former hand area does yield clearer results which are in line with current research on embodiment and agency[153].

Participant data for the McGill Pain scores can be found in appendix C.1, Embodiment scores in appendix C.2 and Proprioceptive Drift measures in appendix C.3.

8.4.2 Individual Results

8.4.2.1 P01

P01's (Group V) pain levels (as shown in Figure 8.11) initially fluctuated for the first 3 sessions before going down to a score of 0.5 out of 5 in session 6. The participant noted that for the first 3 sessions they did not believe that they were controlling the opening and closing of the virtual hand via EMG. P01 stated during their final follow session whilst taking the McGill Questionnaire that "(their pain was) the lowest at the moment for a long time". How-

ever in session 4 after retraining the EMG classifier and producing a more accurate classification file, the participant had greater control of opening and closing of the virtual hand and as a result stated via the embodiment questionnaire (Figure 8.12) that the virtual hand was felt more than before. This can be seen in the embodiment questions from session 3 to session 4 and 5 with the increase in scores. P01 stated in session 4 that "I feel more relaxed during the sessions" attributing this to greater control, which is further stressed during sessions 5 and 6.

Issues with posture in session 8 P01 stated that extra stress affected their pain levels. The pain levels did climb up to 1.5 out of 5 by the end of the intervention sessions (Session 9), before returning to baseline pain levels (2 out of 5) on the first follow up session and 2.5 out of 5 on the final follow up session.

The participant remarked during the first follow up session that before the study their normal pain levels were around 2 out of 5 but during the intervention sessions this significantly dropped with the pain levels raising post intervention sessions. During Follow Up 1 P01 remarked that their pain levels were lower than before the study, leading to Follow Up 2 in which "for two weeks after the sessions with robot stopped I had no pain for 2 weeks". What P01 attributed the raise in pain levels was stress at work but stated "For 30 years I couldn't feel any control of my phantom hand. Being involved in this study has allowed me to regain sensation on my stump (e.g could feel warm water in the shower) before it was numb. Being part of this study has returned my belief I can control the pain and feeling". Also looking at the short McGill pain questionnaire section querying what does the pain feel like; from session 1 to session 9 a decrease in intensity can be observed.

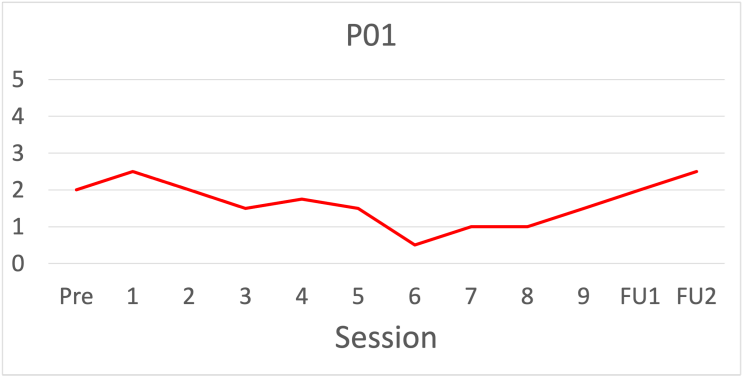


Figure 8.11: McGill Pain score for P01, from baseline to the end of the study (FU2)

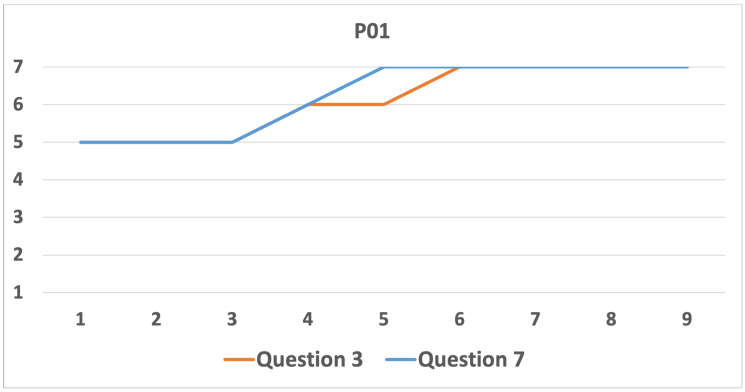


Figure 8.12: Scores for the embodiment questions 3 and 7 for P01, taken at the end of every sessions for 9 sessions.

8.4.2.2 P02

P02's (Group VH) pain levels (Figure 8.13) dropped considerably during the initial sessions and remained at 0 out of 5 for the duration of the study. P03 stated in session 3 that "my little finger (on phantom hand) was stiff, but when the virtual hand opened it became loose, and that my phantom hand became the same shape as the virtual hand". Leading to session 4 in that "Phantom hand is now at the position where my prosthetic hand is located as opposed to be located at the stump". These two statements made by P02 also indicate lowering of pain levels as observed in the pain scores. The participant had very high levels of control opening and closing the virtual hand, due to the selection of muscles for classification. The participant had extremely produced muscles on their lower back on their amputated side used with riding a motorbike to maintain throttle output. Due to the level of amputation these muscles were selected, classified and used for opening/closing the virtual hand which provided 99% classification during training.

The prosthesis the participant used was a cosmetic prosthesis which provided good range of movement on the system. The high scores in embodiment shown in Figure 8.14 does reflect low the pain scores, with only slight variation in pain score values between question 3 and 7. P02 during the final Follow Up session stated that initially there was no pain post intervention sessions, but due to external circumstances at work causing stress the pain did return only to lessen shortly afterwards. "I have more control over the pain, better sleep, overall a huge improvement. I have regained some sensation and control of muscles in the stump. I feel more positive than before starting the study". This highlights the impact control of the phantom hand has in addition to providing strategies in lowering pain spikes.

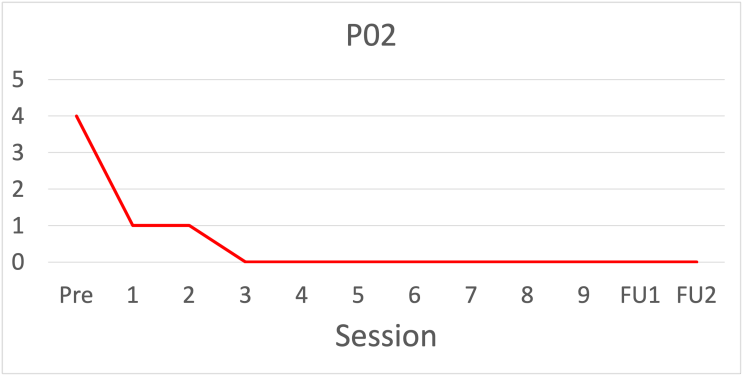


Figure 8.13: McGill Pain score for P02, from baseline to the end of the study (FU2)

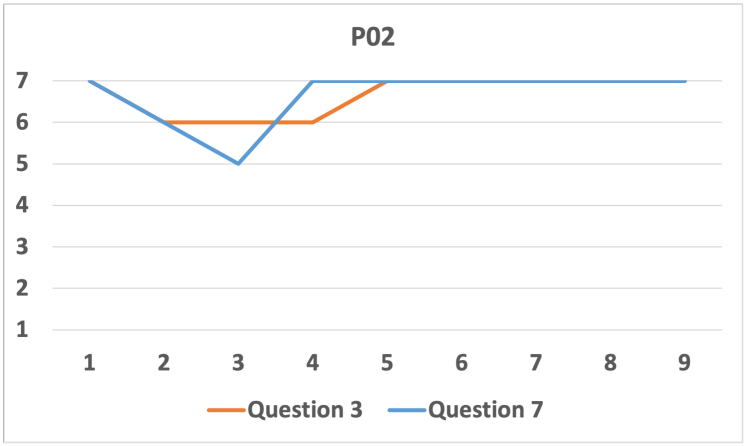


Figure 8.14: Scores for the embodiment questions 3 and 7 for P02, taken at the end of every sessions for 9 sessions.

8.4.2.3 P03

P03's (Group VH) pain levels can be seen in Figure 8.15 which shows extreme levels of fluctuation during the intervention sessions. The participant often left the prosthesis behind in the lab after the sessions, electing to hide the prosthesis in a bag when taking it home. One suggestion to this fluctuation of pain could be due to the low levels of engagement towards the prosthesis in general, which embodiment scores show a maximum of 2 out of 7 during sessions 2-4 (Figure 8.16) which is when their pain levels were at the lowest (1 out of 5). This is before their embodiment scores went to the lowest (1 out of 5) and the pain levels went up from session 6 to 9. The participant's pain levels did return to acceptable levels during the follow up sessions.

P03's embodiment scores for questions 3 and 7 show little variation due to the lack of engagement the participant had towards using the prosthetic limb. Despite this P03 did note for example in session 1 that "Phantom hand aligned with the prosthetic hand. Usually it is not and feels closer to the torso." but general frustration in control and co-ordination lead

to further stress and higher pain levels leading to session 9 in which P03 states "prosthetic is moved across the chest, the phantom hand stays pointing forward", stressing a clear lack of embodiment between P03 and either the virtual hand or the prosthesis perhaps attributable to not regularly wearing one.

Despite the low levels of improvement and no benefits of pain reduction P03 states during the final Follow Up session "The study has improved my awareness and helped with concentration whilst doing exercises. I have not controlled my phantom hand since completing the intervention sessions. Distraction works well in alleviating my pain".

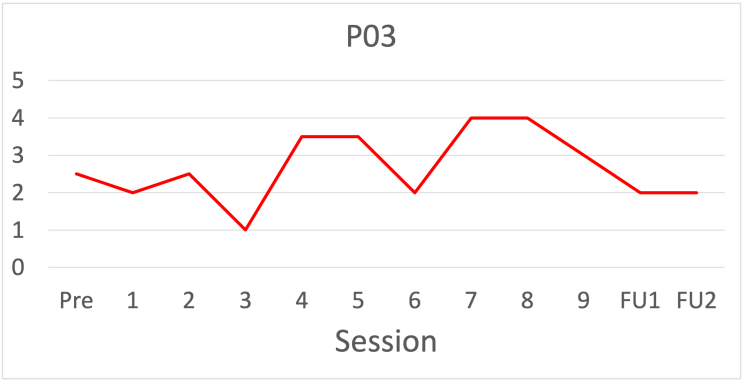


Figure 8.15: McGill Pain score for P03, from baseline to the end of the study (FU2)

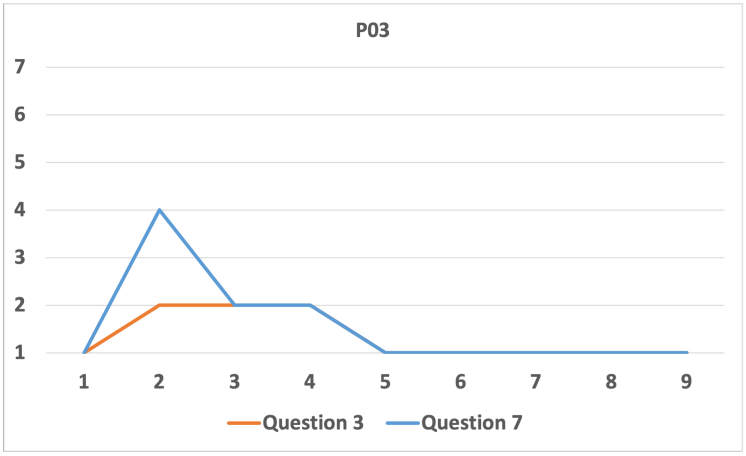


Figure 8.16: Scores for the embodiment questions 3 and 7 for P03, taken at the end of every sessions for 9 sessions.

8.4.2.4 P04

Participant P04 (Group V) Similar to P03, P04 did not use a prosthesis day to day so had to be supplied with a cosmetic prosthesis during the intervention sessions and did not engage with the prosthesis outside the sessions, which may have lead to the fluctuation of pain levels shown in Figure 8.17. The fluctuation of pain is also highlighted in Figure 8.18 also

showing a wide range in scores for questions 3 and 7.

Due to additional injuries the participant felt they didn't have full control of the virtual hand however as stated in session 1 "as I concentrated on the exercise I didn't notice the pain" similarly repeated by other participants. During the McGill Pain questionnaire data aquisiton in session 3 P04 noted "Had a good night sleep, this morning pain was at its lowest ever (1/5). I can relax the phantom arm more and this seems to help with pain" which is also stressed in session 6 "Generally sleep is better than before the study. Phantom hand open and closes when virtual hand does but I have to force it". This statement also reflects the pain levels observed in the pain scores from session 6 to 9 as opposed to the initial pain score from sessions 1 - 5. P04 in session 8 describes the changing of sensations and pain with regards to their phantom hand as "heating up during exercises. Not painful but not nice, stops after exercise, less painful than previous cold feeling". Despite low embodiment potentially P04 could have benefited from longer exposure which will be discussed in the chapter summary. Overall P04 during the final Follow Up session found the study beneficial in terms of different pain (not being as intense and less pain spikes) and better quality of sleep.

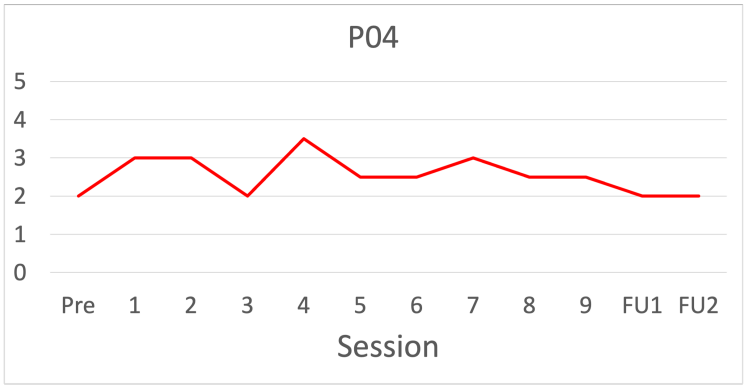


Figure 8.17: McGill Pain score for P04, from baseline to the end of the study (FU2)

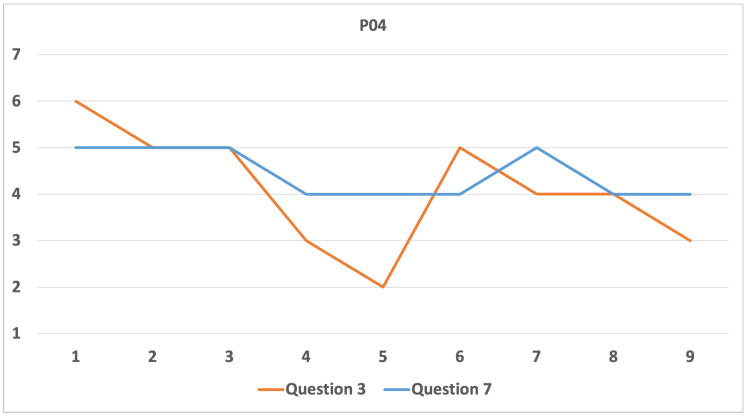


Figure 8.18: Scores for the embodiment questions 3 and 7 for P04, taken at the end of every sessions for 9 sessions.

8.4.2.5 P05

Participant P05 (Group VH) stated a decrease in pain during the sessions, as shown in Figure 8.19. P05 did state during the sessions that "Pain surges and (pain) in general haven't been as bad since starting the study. The area of pain is generally smaller than before study." this despite the participant stating "When doing exercises I can control the phantom hand and it feels where it should be. Haven't had full control of phantom hand since amputation. Pain doesn't change despite full control".

The decrease in pain levels experienced during the intervention sessions were sustained during the two follow up sessions post intervention. P05's perceived levels of pain did decrease to half from baseline levels to the end of the study along with high embodiment scores shown in Figure 8.20. Interestingly there is a decrease in levels from session 4 to 6 which is also observed in fluctuation of pain within the same sessions, before steadying for the rest of the study.

P05 noticed an improvement in control over their phantom hand in session 3, leading to a decrease in pain and in session 5 stating "Pain surges and in general haven't been as bad since starting the study", leading to session 8 in which P05 states that "if pain occurs during the session that performing the movement and grasping/releasing the virtual hand using their own muscles removes the pain."

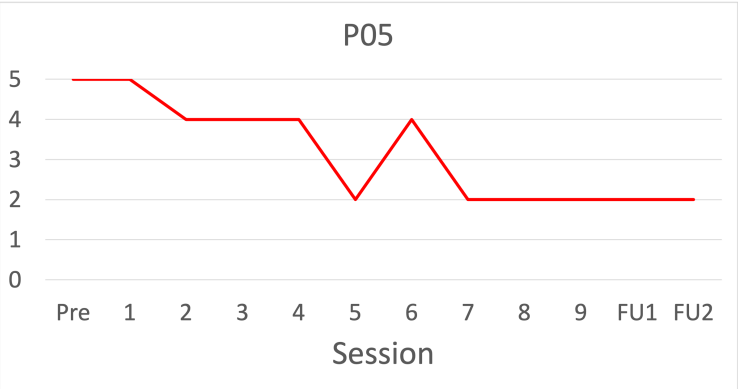


Figure 8.19: McGill Pain score for P05, from baseline to the end of the study (FU2)

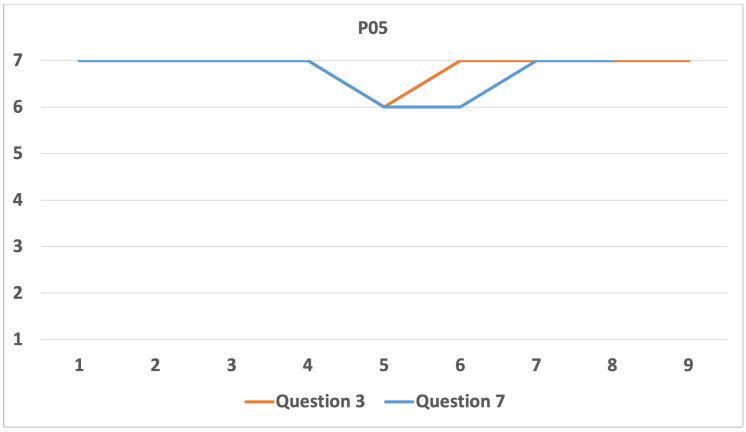


Figure 8.20: Scores for the embodiment questions 3 and 7 for P05, taken at the end of every sessions for 9 sessions.

8.4.2.6 P06

Participant P06 (Group V) who's baseline pain was high (5 out of 5) as shown by Figure 8.21 which reached 3 out of 5 at its lowest point, had their follow up pain going up slightly just below baseline pain levels. Embodiment questionnaire scores shown in Figure 8.22 also fluctuate, however the values for the scores for both questions are the same being the only participant to answer the same values for both questions during the study despite a lack of embodiment.

From the beginning of the intervention sessions P06 noted controlling the phantom hand more than they realised, in particular the thumb from session 2 in which the movement of the thumb was synchronised with the virtual thumb movement, also noting that "whilst grasping/releasing I feel no pain". This is in line with the pain scores as the values are lower as these feelings are present.

Pain scores reported in the diary were higher before sessions e.g. session 3 P06 stated their pain level was 5 out of 5 but after completing of the McGill their pain score was 3 out of 5. Sensations also improved such as with session 4 P06 stating "(phantom arm) feels normal and not cold", with the location of the phantom hand also being reported to be co-located with the virtual hand in session 5 but returning to the stump after completion of the intervention session.

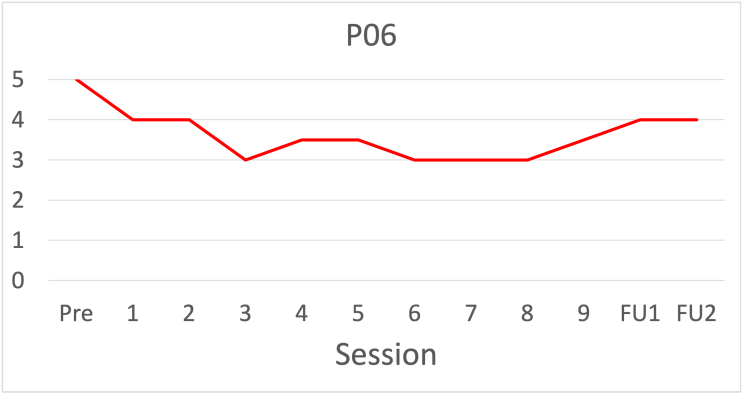


Figure 8.21: McGill Pain score for P06, from baseline to the end of the study (FU2)

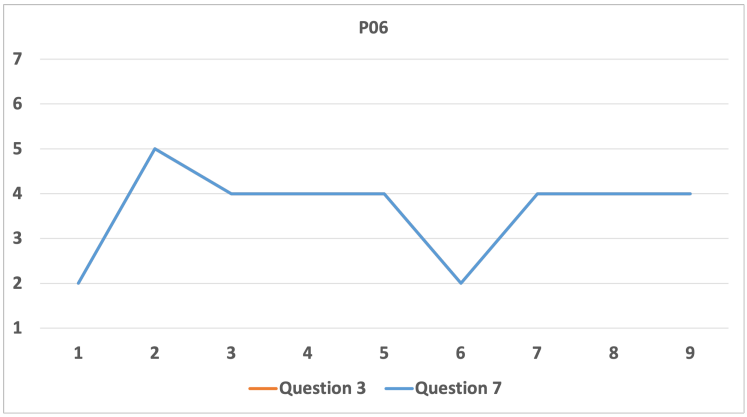


Figure 8.22: Scores for the embodiment questions 3 and 7 for P06, taken at the end of every sessions for 9 sessions.

8.4.2.7 P07

Participant P07's (Group V) pain scores can be found in Figure 8.23 whose baseline pain was 2.5 out of 5, keeping relatively stable until the follow up sessions in which the pain was rated at 1 out of 5 for both follow ups. P07's embodiment scores for questions 3 and 7 can be viewed in Figure 8.24 and do show an initial high score (5) followed by a decrease to 3 by session 3 before increasing for the rest of the intervention sessions. Sessions 2 and 3 pain wise do spike (Figure 8.23) to the participants highest levels during the study although a decrease in scores for the embodiment questions can also be observed this link is casual which requires further research in order to establish. Pain levels after session 3 do stabilise which is also reflected in the embodiment questionnaire scores again casual in nature. Overall P07's pain levels were similar during the Follow Up sessions than before the study. It is worth noting that they were able to control their pain better, feeling that the weather has a big influence on their pain levels (as going away to a country with warm weather, in addition to being relaxed resulted in significantly lowered their pain levels) but stating

they have better control of their arm and feel that they have increased their range of motion since taking part in the study which they believed the study might have helped with pain.

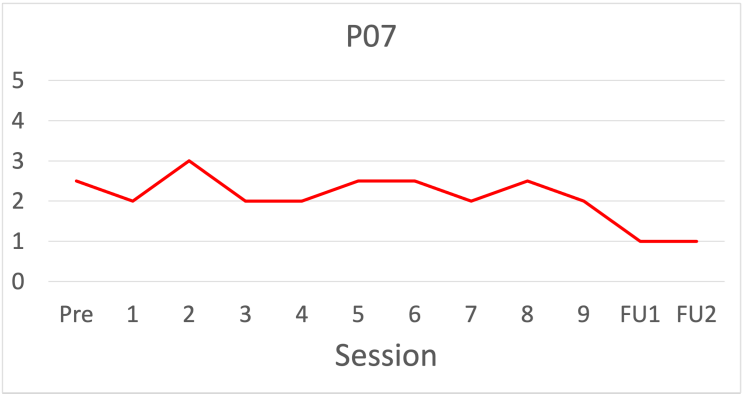


Figure 8.23: McGill Pain score for P07, from baseline to the end of the study (FU2)

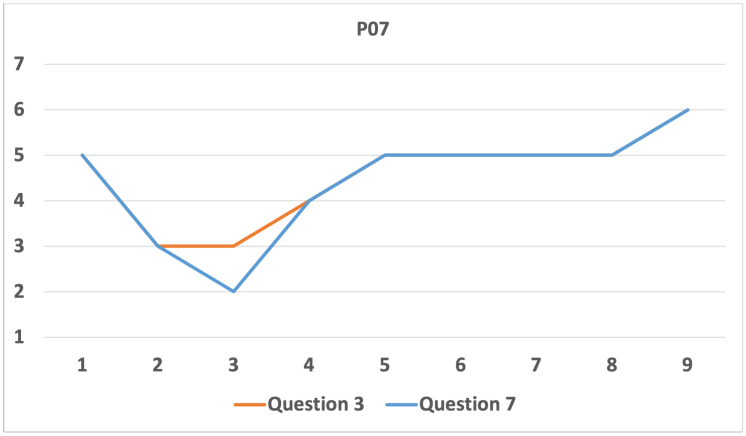


Figure 8.24: Scores for the embodiment questions 3 and 7 for P07, taken at the end of every sessions for 9 sessions.

8.4.2.8 P08

Participant P08 (Group V) pain levels started at 3 out of 5. As shown in Figure 8.25 P08's pain from baseline to session 3 decreased, with a jump observed in session 4, after the weekend break from session 3. Pain levels decrease afterwards to 0 out of 5 from session 7 until the final follow up session in which the pain is reported to be 2 out of 5. High levels of embodiment can be observed in Figure 8.26 which reflect the statements made by the participant. Comments made such as during session 1 regarding the phantom hand being located where the virtual hand was during the session rather than being located in the stump. Although P08 did state their phantom hand was where it should be but over a period of time their hand went back to the stump.

During the course of the intervention sessions P08 did notice the time their phantom hand was located in the correct position lasted longer before retracting to their stump. This

suggests that the participant was embodying the virtual hand as their own, again reflected in the embodiment questionnaire responses. With regards to the position of their phantom limb P08 did indicate that when their phantom limb was located where it should be, the pain was lower than normal, and once their hand returned to the stump the pain levels were back to normal the levels usually experienced. Session 4 shows a spike in pain levels (Figure 8.25) which P08 attributes to the cold weather, and also the start of the second week of intervention sessions which could explain this spike.

During session 7 in which pain levels returned to zero the participant stated "The robot sessions lower the pain better than any medication, and for longer". This is further demonstrated when after session 8 the participant felt "blood rushing to the left (amputated) hand" despite the cold weather P08 stated that his pain was less, and when pain spikes occur they close their eyes and moved their arms as if doing the exercises to bring the pain levels down quicker. During the final Follow Up session P08 stated that they had reduced their ad hoc pain medication as a result of their lower pain levels but was still taking their prescribed medication.

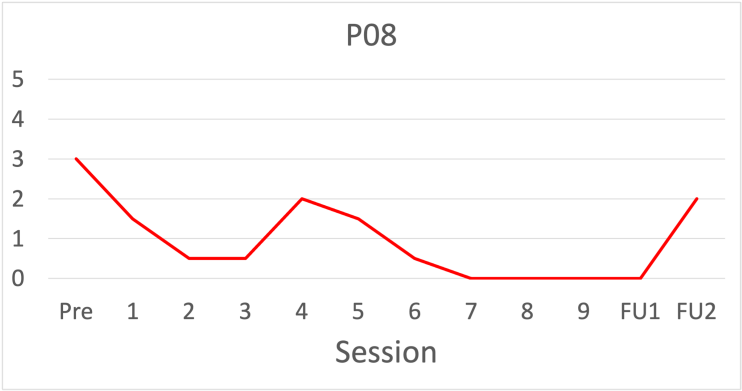


Figure 8.25: McGill Pain score for P08, from baseline to the end of the study (FU2)

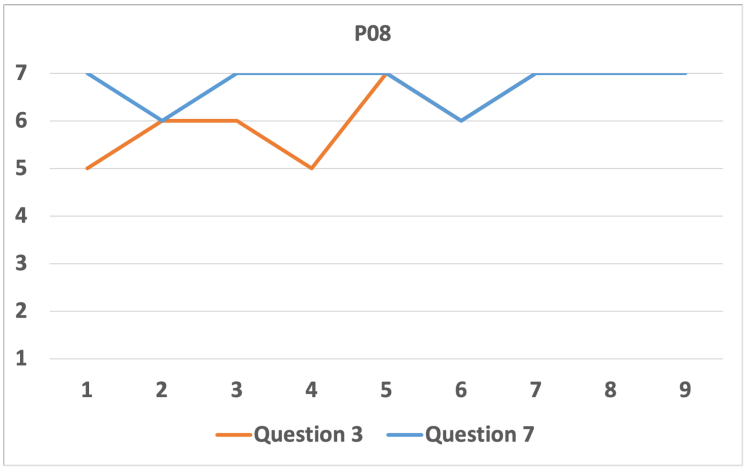


Figure 8.26: Scores for the embodiment questions 3 and 7 for P08, taken at the end of every sessions for 9 sessions.

8.4.2.9 P09

Although P09's (Group VH) pain levels (Figure 8.27) quickly went to 0 out of 5 (end of Session 2) there is a jump in pain shown in session 7, which the participant attributes to "over working the limb during the weekend". The reported pain levels go back down to 0 and stay constant until the end of the study.

Interestingly P09's embodiment questionnaire scores for questions 3 and 7 (Graph 8.28) does suggest confusion between the questions as shown in session 4 and session 6. Also a decrease in question 3 score for session 7 does reflect the perceived pain spike also observed in sessions 7. Before taking part in the study P09 stated that they would not be able to wear a prosthetic due to the sensitivity within their stump, the configuration of the system allowed them to take part in the study.

When P09 experienced Phantom Limb Pain the pain was located in the fingers as an aching pain and stabbing pain in the palm of the phantom hand. The feeling of embodiment was high (Figure 8.28) and during session 8 P09 stated that they "felt the block pushing on the missing hand as they were pushing the block" which is reflected in the high embodiment scores for session 8 and in general for this participant.

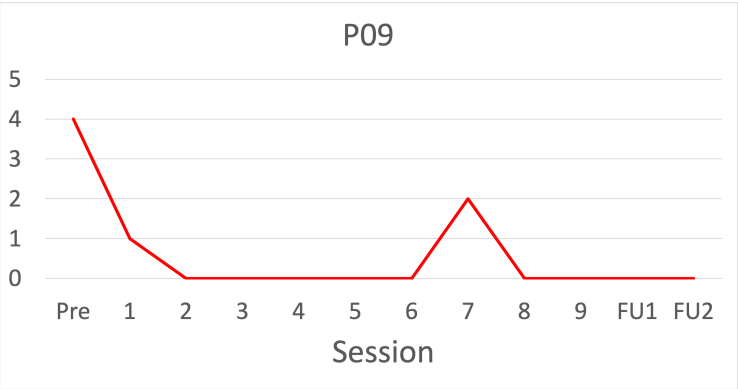


Figure 8.27: McGill Pain score for P09, from baseline to the end of the study (FU2)

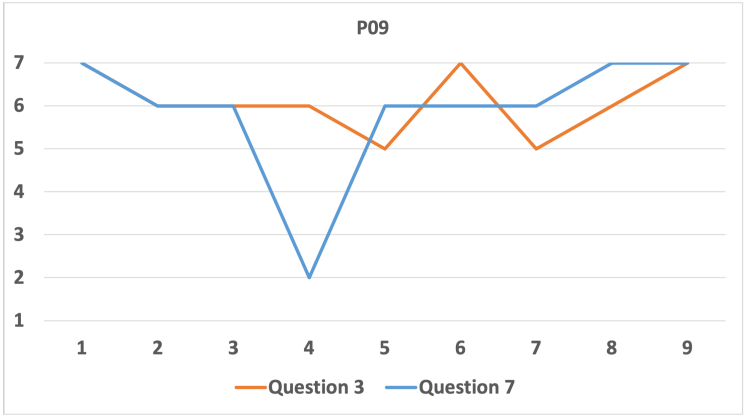


Figure 8.28: Scores for the embodiment questions 3 and 7 for P09, taken at the end of every sessions for 9 sessions.

8.4.2.10 P10

Participant P10 (Group V) who's pain level on baseline was 2.5 out of 5 as shown by Figure 8.29 experienced fluctuating levels of pain during the study. However it was noted that before the study their sleep was affected by the Phantom Limb Pain and during the study their sleep and subsequently their mood and pain levels improved. Despite fluctuating levels of pain, P10's embodiment questionnaire scores for questions 3 and 7 (Figure 8.30) are scored very high, with question 3 seemingly following the pain levels between session 2 to 5 and again from session 6 to 8. Initially P10 experienced strong levels of embodiment stating in session 1 "Came here in pain, leaving with no pain. Felt as if the virtual arm was my own, could high five virtual arm" and generally viewing the intervention sessions as a pleasant experience. This could be attributed with the high levels of embodiment to the extent that P10 during session 5 highlighted "When I laughed, I saw/perceived my left arm shaking as it would if it were present whilst laughing". Sleep levels were also improved as stated by the participant which in turn improved their mood. During the Follow Up sessions P10 stated that their pain levels were lower than before the study, along with a better mood and quality of sleep, increased sensation in their stump also being more aware of exactly were their pain was and had more control in terms of lowering pain when pain spikes occurred.

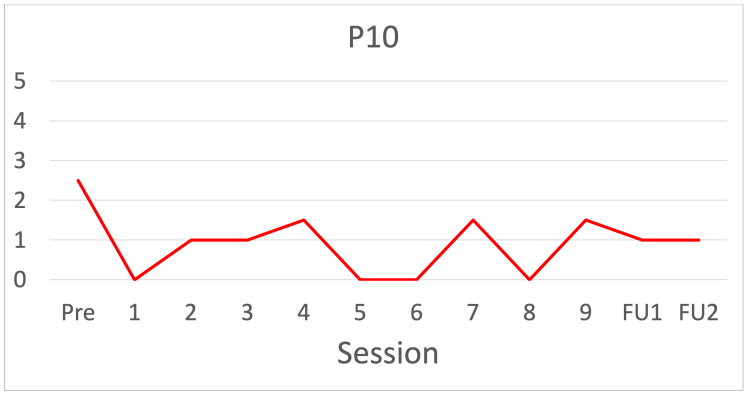


Figure 8.29: McGill Pain score for P10, from baseline to the end of the study (FU2)

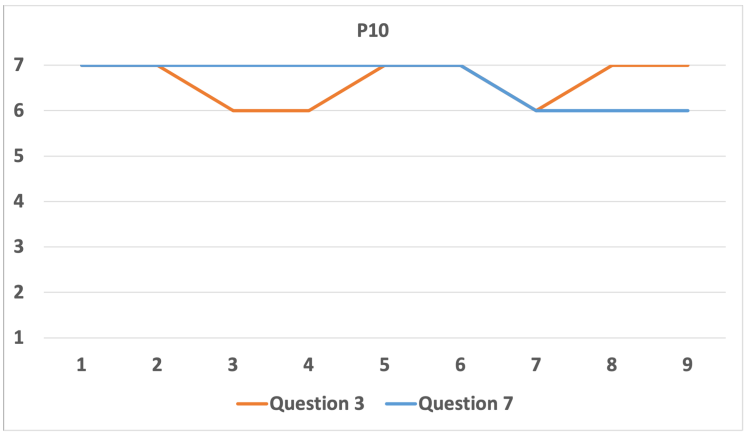


Figure 8.30: Scores for the embodiment questions 3 and 7 for P10, taken at the end of every sessions for 9 sessions.

8.4.2.11 P11

Participant P11 (Group VH) who's pain levels dropped to 1 out of 5 until session 6 and further dropped to 0 out of 5 until the end of the intervention sessions (Figure 8.31). The reported pain levels during the follow up sessions did increase to a maximum of 1.5 out of 5 at the last follow up session (Figure 8.31). There is a significant difference in embodiment scores for questions 3 and 7 shown in Figure 8.32, with question 7 scores fluctuating as opposed to question 3 scores between sessions 1 and 5. P11 sensitivity to cold weather was highlighted several times during the intervention sessions. During session 6 in which the pain was the lowest it has been since amputation, P11 stated that the stump "now feels warm instead of cold" by session 8 the warm sensation was lasting longer. During the Follow Up session P11's pain was mild, along with a calmer mood with improved sleep and also wearing their prosthetic limb more frequently than before the study.

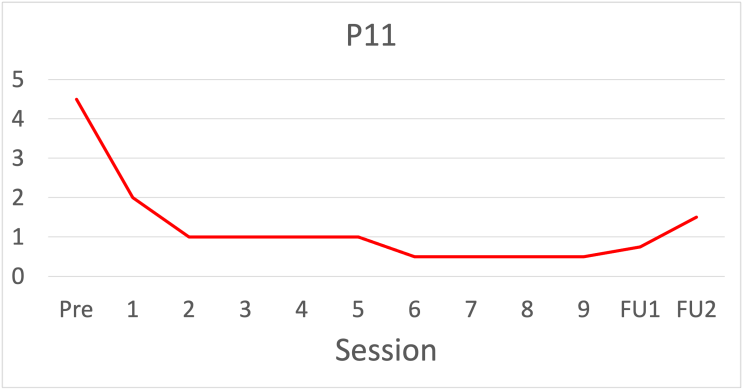


Figure 8.31: McGill Pain score for P11, from baseline to the end of the study (FU2)

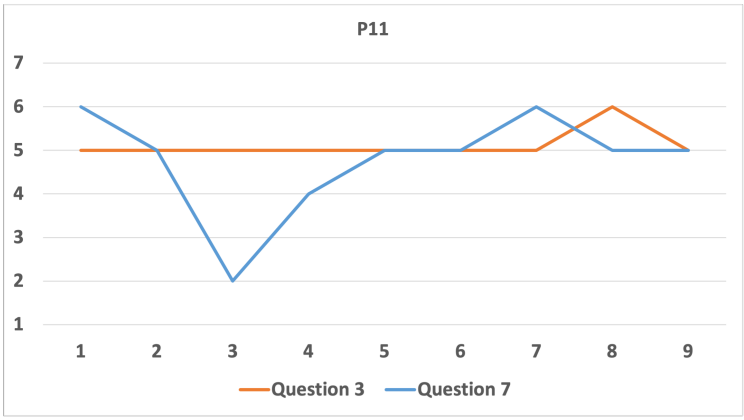


Figure 8.32: Scores for the embodiment questions 3 and 7 for P11, taken at the end of every sessions for 9 sessions.

8.4.2.12 P12

Participant P12 (Group VH) whose pain scores during the study can be seen in Figure 8.33, which fluctuated greatly during the intervention sessions. Despite the reported pain level after session 5 being 2.75 out of 5, the pain levels were reduced to 0.5 out of 5 after session 8. The participants pain levels did go up after the intervention sessions to 1.5 which was the same score as baseline pain, lowering down to 1 out of 5 for the final follow up session. Similar to P11, P12's embodiment scores for questions 3 and 7 (Figure 8.34) significantly fluctuate even between the two questions which is also reflected in the perceived pain scores. As observed in both the pain scores and embodiment scores the varied range can be attributed to P12's lack of muscle control as stated in session 2, these comments continue but despite the pain scores going to nearly 3 in session 5, the participant commented that their pain was generally better since wearing a prosthetic since just over a month before session 5. In general P12 noticed a positive effect on their pain levels in between intervention sessions and their pain spikes are not as bad as before the study. Range of movement and their arm strength improved which

enabled P12 to wear their prosthesis more which also helps with regulating their pain levels.

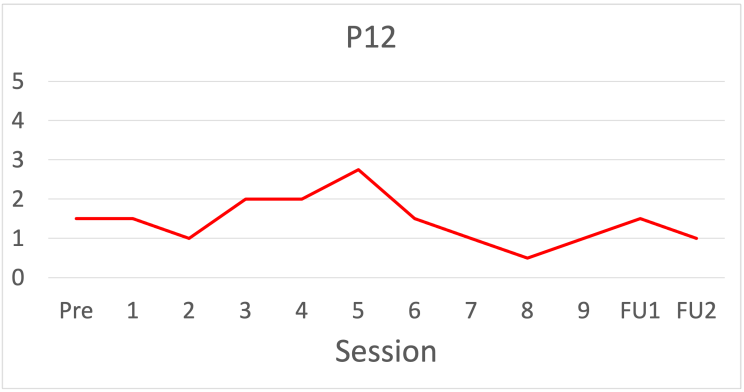


Figure 8.33: McGill Pain score for P12, from baseline to the end of the study (FU2)

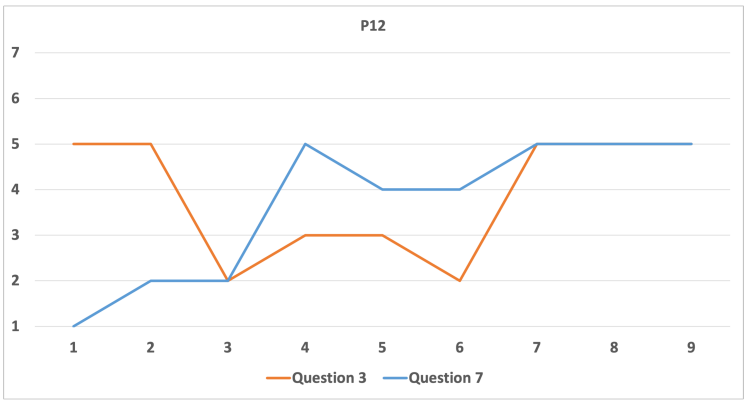


Figure 8.34: Scores for the embodiment questions 3 and 7 for P12, taken at the end of every sessions for 9 sessions.

8.5 Chapter Summary

This Chapter has described a feasibility clinical study with twelve upper limb amputees suffering from Phantom Limb Pain, to which the system has had a positive effect as reported by the pain questionnaires and remarks made through the intervention and pain diaries. This is regardless if participants received VR with haptic feedback or VR only, however due to the heterogenous population recruited into this study it is hard to draw concrete conclusions on the impact haptics had on pain relief. This does feed into future studies which could be conducted based on a more selective inclusion criteria, longer monitoring of pain levels post intervention and the use of frugal home based versions of the system complementing a full size system in the clinic.

In terms of pain scores obtained via the McGill Pain questionnaire, decreases could be observed in the participant population. One criticism of the protocol described in this Chapter is that the questionnaire is taken at the end of the intervention sessions, and

therefore is only a brief snapshot of what the participants were experiencing post intervention. Although this was compensated by data extracted from the pain diary, the questionnaire could also have been taken before the intervention to provide a better measure of the intervention on a session to session basis. One aspect mentioned by participants is that by talking about their pain their pain levels often went up, this in addition to the questionnaires only providing a brief snapshot into pain at a specific moment highlights the importance of pain diaries. Observational data from the pain diaries and feedback from intervention and follow up sessions have been included in the individual results, but give a unique insight into more than just pain levels. Some of the information provided in pain diaries include:

- That even if pain levels did not decrease other improvements such as mood, sleep, range of movement, control of their phantom hand were observed.
- Importantly, the study as stated by most of the participants provided them the tools or strategies to help lower their pain if pain spikes occurred. This includes visualising and physically performing arm movements along with using residual muscles to open/close their phantom hand.
- Participants such as P03 and P04 despite not showing a benefit in terms of pain scores gained a better understanding of their pain, allowing them to put their experience into context and seek further treatment for their pain.
- Mood and sleep has an effect on pain as highlighted by participants most notably P01 and P02 who's pain decreased during the intervention sessions but stated during the post intervention period their pain increased which they attribute to stress and anger issues.
- Those who used a prosthesis fitted pre study utilised their prosthesis more, and those that used cosmetic prosthesis actively pursued acquiring and using a functional or myoelectic prosthesis (P08 and P11).
- As a result of engaging muscles in their affected arm whilst performing movement participants also experienced better muscle definition in the stump. This was highlighted by participants to leading to more confidence but also might lead to potentially lower risks of stump neuromas as highlighted in Chapter 4.

As with any study there are limitations, the previous mentioned heterogenous population

recruited into this study feasibility clinical study and issues properly balancing groups clearly had an effect on the results. Additional injuries such as brachial plexus lesions due to the nature of participant's accidents resulted in alterations being made to the software in terms of scaling movements. Other limitations include:

- Some of the participants (P03,P04,P10 and P12) could have benefited from more intervention sessions, issues such as the number of intervention sessions in order to embody the virtual limb were hampered by factors such as participants either not wearing a prosthesis or limited use wearing one. Potentially these participants could see a reduction of pain if they were offered more exposure to the intervention.
- This leads into the spread of the sessions, in the protocol 3 sessions per week were approved. Participants such as P01, P03, P04, P05, P06, P08 and P12 all saw spikes in their pain scores taken in session 4, which is the start of the second week. Interestingly the spikes observed at the start of week 3 (session 6) seems to be less pronounced. Potential factors for this could be a maximum of a 4 day gap between sessions 3 and 4 and external factors such as participant activities (e.g. P09 using their amputated limb moving heavy boxes) outside the intervention sessions. This inter week pain spike is clearly observed in Figure 8.4, however the fact that the spike is lower at the start of week 3 as opposed to the start of week 2 does suggest the intervention is having an effect on pain levels, again suggesting a more detailed future study involving a hybrid in-clinic/home based system should be given consideration.
- The protocol allowed follow up measurement sessions 3 and 9 weeks after intervention sessions to determine if pain levels have been sustained. This provides a medium time frame to study, future studies conducted should consider much longer periods of time to examine pain levels over months to years post intervention.

Regardless of the group either experiencing haptics or not the intervention did provide pain relief and both enhanced embodiment and the sense of agency (Section 8.4). The inclusion of haptics can not be statistically determined to play the defining role in this study in terms of pain relief. However as a feasibility study and feedback from participants, increasing the sense that they were interacting with the environment did contribute to participants believing that the virtual limb was theirs. Future studies conducted in this field could employ method-

ologies such as a crossover study, to provide a clear picture of what haptics brings in terms of pain relief compared to no haptics. Frugal home based systems which could be purely a virtual reality system could complement a clinical system that utilises haptics, allowing participants to experience haptics in the clinic and use a home based system for ah hoc pain relief.

Chapter 9

Impact of the research & Conclusions

9.1 Novelty of the Research

This thesis has focused on combining immersive-virtual reality with haptic robotics for the treatment of Phantom Limb Pain. Although immersive VR has been utilised in reducing acute pain in several pain populations [124] and is now FDA approved for chronic pain reduction [223] the system proposed in this thesis is the first to evalulate the clinical feasibility of combining VR with haptic feedback for the reduction of perceived Phantom Limb Pain.

The addition of haptics is crucial in closing the action perception loop, visually participants can see an arm, proprioception from the participant moving their limb in space reinforces agency and to an extent embodiment. Haptics provide the sensation of touch between the arm and objects via interactions, which is key as sensory primary afferent fibers which convey touch and pain [224] within the spinal cord are involved in the ascending and descending pathways from the brain. This addition of haptics therefore attempts to correct painful stimuli via closing of the action perception loop [225]. The feasibility clinical study reported in this thesis showed that participants experienced a decrease in perceived levels of pain. In addition, the use of the system did not show negative effects as stated by participants when proving feedback during the final follow up session (Chapter 8.4.2). Participant comments from follow up sessions/pain diary entries also highlight:

- Those who experienced haptics (P02, P05, P09 and P11) stated that they felt the virtual limb was their own limb earlier in the intervention sessions as opposed to those who did not experience haptics (P01, P04, P06 and P07).
- This lead to better control of their phantom hand and observations by participants that their pain levels felt lower and their pain spikes were not as intense (P01, P02, P05, P06, P07 and P09).
- In addition to better control of their phantom hand, co-location between their phantom

hand and where their missing hand was better and periods when this happened were longer for those who experienced haptics (P05, P06, P07 and P08).

Overall more research and better formalised clinical studies are required to draw any concrete conclusions. Incorporating elements from this thesis work to create bespoke rehabilitation therapies, could potentially in the future use neurological measures and brain imaging techniques to investigate cortical reorganisation to further shed light on the mechanisms of Phantom Limb Pain.

9.2 Contribution to the clinical understanding of Phantom Limb Pain

Due to the complexities underlining Phantom Limb Pain, few direct contributions can be drawn from the thesis when applied to furthering understanding Phantom Limb Pain or the mechanisms behind it. However the fact that both groups experienced decreased perceived levels in pain, to which some participants attribute to believing that the actions they were acting performing (grasping/releasing of their missing hand) does suggest that agency might part (Chapter 6, Section 6.4).

Although participants were blinded to the group assignment, the experimenter was not, potential bias effects were minimised as much as possible by attempting to balance groups. Establishing study designs which completely remove the placebo effect prove difficult even when using a control group which this study implemented. All participants experienced the exact same intervention bar one variable, haptic feedback. At no point were participants told which group they were in.

The heterogenous population recruited into this feasibility clinical study presented in thesis proves a difficult point in designing a clinical study. One suggestion could involve restricting the inclusion criteria to a single amputation level and to double blind the study or perform a cross over study (in order for both groups to experience haptics and to observe exactly how much haptics provides in potential pain relief over a non haptic intervention) which could be considered for intermediate studies in the near future.

- Agency or "functional embodiment" might play a part in enabling an amputee in believing a virtual or prosthetic limb is theirs.
- The research presented in this thesis do support views that the connections within the brain are not simply "rewired" post amputation. Evidence of this comes from P01 and P11 who reported that they were able to experience sensation on their stump and missing (phantom) during the intervention sessions, despite never experiencing these feelings after their amputation.

9.3 Contribution to the understanding of treating Phantom Limb Pain

The research reported in this thesis does suggest a viable alternative in terms of effectiveness to pharmacological based therapies without any observed short or medium term negative side effects.

- With regards to pain decreases regardless of the group, decreased pain levels are better sustained in those who experienced VR and haptics (Chapter 8, Section 8.4.1).
- It is clear that current pharmacological treatments are not effective [144] as a sole pain reduction therapy, with the majority of participants finding their prescription ineffective. However since this thesis study asked the participants to continue their prescription the impact of withdrawing the medication on this paradigm is not known. One participant (P08) did stop taking ad-hoc medication altogether during and after the study.
- Despite its ineffectiveness when it comes to perceived pain reduction as per the above point. Pain medications, such as Gaba-based medicines, which don't reduce loss of touch or proprioception may impact less on the effectiveness of a haptics based system less than those that do. [143][100] resulting in potentially better outcomes for the participant.
- The system could potentially be used in the early states of the amputation process (or even before a known amputation date is due to take place if the amputation is a non traumatic direct amputation) and could shorten advanced steps in the process like EMG recognition if an amputee chooses to have a myoelectric prosthesis. Due to the immersive virtual reality paradigm, the system enables those with poor ROM to start

rehabilitation due to movement scalars applied to virtual movements with the immersive aspect ensuring that the participant is not fully aware of their ROM restrictions.

- As mentioned previously, any treatment for Phantom Limb Pain should be custom tailored to the patient due to the unique attributes that arise due to an amputation, in terms of pain (Chapter 4.2) and severity of the amputation and if a prosthesis is required.

9.4 Contribution to the use of technology relating to Phantom Limb Pain Treatment

Technological advances other than visual based systems has been making inroads into the field of rehabilitation for upper limb rehabilitation. The addition of haptics applied to an immersive virtual reality system as a treatment paradigm in this thesis has yielded some observations and contributions.

- The importance of anatomically correct inverse kinematics can not be stressed enough. Many virtual reality systems and previously mentioned amputee based systems due to the complexity of implementing this element forego this step and simply place "floating hands" as a substitution. This is counter productive in terms of decreasing embodiment and potentially increasing pain levels as discussed in Chapter 6 (Section 6.4). This step does require tuning fine details, that participants did notice, pointing out that "the arm position/orientation did not feel right" before corrections were made. Ensuring that the inverse kinematics seems anatomically correct, was one of the critical technical developments presented in this thesis. Correct kinematics should be paramount when developing immersive therapies for the future.
- Haptic effects where possible should be included in systems for upper limb therapies. Although the effects and usage of haptics in this thesis are considered to be simple compared to other haptic based systems, it is clear from those who experienced the haptic effects that they added to the immersiveness of the experience. During one of the sessions a participant (P02) who experienced haptic effects in their notes remarked that they "could feel the the shape and texture of the cube (which the participant said felt like wood) in their missing hand". Another participant (P12) who also experienced haptics stating they "felt blood rushing around their missing hand

(after a session) when their amputated arm was hanging freely". These examples highlight the effects haptics had on the participant's phantom limb sensations.

9.5 Lessons from the research and future work

Purely examining levels of embodiment from a questionnaire or drift measurement taken traditionally for a single session does not seem to be a good indicator of success. This is highlighted by participants (P03, P04, P07, P10 and P12) with low embodiment scores during the intervention sessions stating they felt they had better control and co-location of their phantom hand. Focusing on not just embodiment scores but looking at long term position and control of the phantom hand might yield better reporting of levels of embodiment and ownership due to the overlap of embodiment/agency/functional embodiment (with haptics) and promoting improved and correct motor command of the phantom (see appendix E.2).

Both technical and clinical lessons have been learnt from the process of this research which could be considered in future work. These include:

- Tailoring the sessions more around the participant. In terms of number of sessions (some participants required less than 9 sessions, some would require more) and also in spreading them out evenly during the weeks. This was highlighted in the pain spikes observed in participant pain scores (Section 8.4.2). Some participants might require more intensive schedules whilst others might benefit from a more relaxed approach.
- An approach that might support the combination of intensive therapy such as the one proposed in this thesis in the clinic with simple interactions at home. This could also potentially increase the number of participants benefiting due to the time requirements along with travel constraints and provide tools in the home environment from such interventions.
- Although care was taken to implement a range of different exercises via gamification, more attention should be paid in the future to create a greater range of exercises and also compatibility for those with ROM limitation, taking into consideration any future home based exercises.
- During rehabilitational centre sessions more streamlined measures such as EEG pickups along with regular MRI scans should be considered. Focusing on data

collection to investigate cortical reorganisation could lead to two outcomes; 1) a greater and more in-depth understanding on what is happening in the brain during these perceived pain decreases (or increases) which could potentially lead to a greater understanding into the mechanisms of Phantom Limb Pain; and 2) potential optimisation of the therapy to examine which exercises if any greatly benefit the participant over others and using this information as per the previous points to tailor the therapy to the individual. This could also prove interesting when comparing cortical maps of those amputees who do not experience Phantom Limb Pain against a population of those who do experience pain to see what areas of the brain are more or less active.

- Working more with clinicians involved in the whole rehabilitation process in order to better tailor the system to the individual needs. As eluded to above the system could potentially be used early in the amputation process or before the amputation if planning takes place. The benefit in using a virtual reality system is that the system could be changed to deliver different and targeted visual and haptic cues to allow aspects such as parts of the upper limb visually fading at the point of amputation to mentally prepare the patient, visually replace the limb/part of the limb with a standard prosthetic limb or myoelectric prosthetic. In addition to the visual information and "look" of the prosthesis this could be achieved more realistically due to the system utilising haptics to add the weight of the prosthetic device, and provide accurate simulation of the prosthesis dynamics with potential EMG activation for grasps/release. This could enable the system to train the patient to use a varied range of prosthetic limbs enabling a more efficient process overall but also realistically setting patient expectations which could potentially lead to a higher limb use and improve engagement whilst wearing a prosthetic limb.
- Although the majority of the time the bipolar electrodes worked with the participants, due to the nature of the injuries some participants had problems with the classifier which had to be retrained multiple times. It could be argued that a greater number of electrodes should have been used in order to minimise cross over etc however to keep interactions simple and reduce setting up time the system only utilised simple binary grasp and release. Adding further electrodes would in some cases increase accuracy

and ease of use for some participants but would also increase the time setting up and removing equipment. A balance should be met again tailoring the system to the user.

- On a technical point although the use of Unreal Engine has enabled fast development of the system and includes a solid support for an increasing range of hardware; it does suffer from constant patches and bugs. The version of Unreal Engine the system used in the study was 4.10 with the current as of writing release being 4.19, 9 updates within two years which in some cases requires complete rebuilding of custom plug ins or major revisions of workflow and pre-existing methods used in the running of the system.

9.6 Conclusion

The results presented as part of this thesis research have shown that the intervention developed can decrease pain levels in upper limb amputees. Both groups showed a decrease which is not unusual to the the fact both groups experienced a form of intervention. At no point were the participants told about force feedback via haptic interaction. All twelve participants thought that they were experiencing the full system, resulting in minimising any placebo effects and ensuring the experience, on the face of it was the same for everyone bar the inclusion of force feedback for half of the participants. As with any experimental intervention, there might be other factors such as excitement to be taking part in the study; the location of the sessions, or other prescribed interventions as part of ongoing treatment plans (e.g medication) that could potentially have an impact on the results and contribute to the placebo effect. Unfortunately these are difficult to account for in this research. It is assumed therapies such as the one proposed in this thesis should be considered as adjuvant to other interventions. The experience stemming from individual participants and the positive results of the non haptics group does suggest that; a more tailored therapy schedule could be implemented for a particular participant, such as once a week robot therapy in combination with a home based VR only solution.

In terms of reflecting the results on the hypothesis and objectives, statistically there was no obvious difference in the groups, however the low participant numbers coupled with the complexities of amputation might contribute to this result.

Phantom Limb Pain is complex, severely effecting the lives of those who suffer from

it, made worse by the uncertainties that underline the condition and the range of treatment options with varied success, with sufferers opting to try anything to alleviate the pain. Most of these treatments have both long and short term side effects.

Neuroscience has potentially lead to deeper understandings behind the mechanisms of Phantom Limb Pain, despite theories often seeming conflicting are also often complementary, but hampered by the complexities that are caused by an amputation, in particularly an amputation which was caused by traumatic means which could also involve additional injuries.

This research builds on the foundations of visual surrogate therapy, a known treatment paradigm with varied success and combines the novel approach of haptics in order to further immerse the participants in the virtual environment/task.

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Appendix A

Published Papers

Snow P.W. , Loureiro R.C.V. (2013) Rehabilitation of Phantom Limb Pain Using an Immersive Robotic Sensorimotor Training Paradigm. In: Pons J., Torricelli D., Pajaro M. (eds) Converging Clinical and Engineering Research on Neurorehabilitation. Biosystems & Biorobotics, vol 1. Springer, Berlin, Heidelberg

P. W. Snow, R. C. V. Loureiro , "Design of a robotic sensorimotor system for Phantom Limb Pain rehabilitation," 5th IEEE RAS/EMBS International Conference on Biomedical Robotics and Biomechatronics, Sao Paulo, Brazil, 2014, pp. 120-125.

P. W. Snow, I. Sedki, M. Sinisi, and R. C. V. Loureiro, "Robotic therapy for phantom limb pain in upper limb amputees," 2017 International Conference on Rehabilitation Robotics (ICORR), London, 2017, pp. 1019-1024.

Peter W. Snow, Dace Dimante, Marco Sinisi, Tom Quick, Richard Comley and Rui C.V. Loureiro. "Immersive Robotic Therapy for the Treatment of Brachial Plexus Pain", Frontiers in Neurology, Automations in Long-term Neurorehabilitation, In Review.

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Design of a Robotic Sensorimotor System for Phantom Limb Pain Rehabilitation*

Peter W. Snow, *Member, IEEE* and Rui C.V. Loureiro, *Member, IEEE,* Richard Comley

Abstract— **The use of robotics in rehabilitation has shown to have a positive outcome when applied to stroke patients and other movement based therapies. Despite recent studies looking at these types of therapies in helping patients with Phantom Limb Pain very few have looked at employing the elements that make robotics successful with stroke patients towards amputees. Phantom Limb Pain affects the majority of amputees, resulting in the need for further study due to the vast range of potential treatments available. This paper examines the effects of Phantom Limb Pain, its treatment, paradigms based on robotic rehabilitation, and provides an outline of a possible therapy method based on an immersive system providing proprioceptive and kinaesthetic feedback to the user while performing a manipulation task.**

I. Introduction

Losing a limb through amputation, regardless of the cause, is a traumatic experience and as a result all attempts are made to salvage the limb [1]. Amputation poses physical effects, such as learning how to live with a prosthesis, the loss of the limb and subsequent pain post amputation. It also affects mental wellbeing such as coping with the limb loss, the psychological trauma and chronic pain effects imposed by phantom/residual limb pain. It is this combination of both physical and mental effects, which makes the subject of amputation, inter disciplinary, and provides a varied range of research topics.

In recent years the issues and exposure of amputation have been accentuated due to prolonged wars such as, the Afghanistan and Iraq campaigns, primarily as a result of improvised explosive devices [2] [3] [4]. This has lead to a spur in research focusing on improving limb salvation via improved battlefield armour, medical procedures and post amputation aspects such as prosthesis design and improved rehabilitation. Although this surge in development is based on military background, the effects are now being transferred to civilian use. This coupled with lessening cost of sensors, computing and robotics combine to create avenues of research that wasn't possible a decade ago. By using various techniques and subject areas, questions that have remained unanswered, such as phantom limb pain could in the foreseeable future yield results [5].

Although the use of robotics in rehabilitation is not new, the use of haptic therapies in the investigation of how cortical reorganisation is affected by phantom limb pain is still in its infancy. This paper focuses on the area of haptic neurorobotics and suggests how therapies based on proprioceptive feedback can be used to treat phantom limb pain and how it can affect cortical reorganisation during rehabilitation.

II. PHANTOM LIMB PAIN

The Phantom Limb phenomenon was first coined by Mitchell in 1872, to describe the sensation that an amputated or missing limb (even an organ, like the appendix) is still attached to the body and is moving appropriately with other body parts [6]. Pain as a result of Phantom Limb phenomenon (also called phantom limb pain) and has been reported to be present in 50-80% of amputees with implications to the quality of life of those experiencing the symptoms [7]. Pain can have a negative effect on the rehabiliation outcome due to varied mental/physical symptoms (e.g. wetness/burning/locking sensations) and the lack of evidence explaining why the symptoms persist. Recent work on the diagnosis and treatment methods in Phantom Limb Pain highlights the sensation of pain as overlapping with specific brain areas during movement onset[8]. Previous Phantom Limb Pain treatments have included further amputation of the already amputated limb. Although some of these radical treatments seem to have some positive effects, the Phantom Limb Pain often returns and in some cases more aggressively than before.

Ramachandran and Hirstein's [9] work showed how the plasticity of neurological connections mapped touch and sense affected Phantom Limb Pain. As a result Ramachandra's team conducted a simple experiment with a mirror box, which helped alleviate Phantom Limb Pain both in the short term and long term with some of the participants of the experiment. This has lead to research into virtual mirror box type studies by Cole & Murray [10] to name but a few. Recent work looked at not only replicating Ramachandran's [9] mirror box using virtual reality but also have explored the neurological aspects of the mirror box use,

Peter W. Snow and Richard Comley are with the School of Science and Technology, Middlesex University, London, UK {p.w.snow/r.comley}@mdx.ac.uk

Rui C.V. Loureiro with the Aspire Centre for Rehabilitation Engineering and Assistive Technology, University College London, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, HA7 4LP, UK r.c.v.loureiro@ieee.org

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using modern imaging techniques such as Magnetic Resonance Imaging [11]. These modern imaging techniques have proved essential [8] into gaining a deeper understanding and interpretation of the unsolved parts of the Phantom Limb Pain phenomenon.

The notion that cortical reorganisation is responsible for phantom limb pain has been put forward by Weeks and colleagues [12] and backed up by studies carried out by Lotze [13] and Flor [14]. Although these studies show a possible origin relating to phantom limb pain, the work carried out by Tsao and colleagues [12] have postulated the concept of proprioceptive memory. This theory is based on the view that the brain keeps possession of a memory of specific limb positions and that post amputation results in a conflict amongst the brain and visual system. This concept is tied into our approach in that we investigate how virtual systems can affect cortical reorganisation.

A recent publication [15] reviewing various phantom limb pain treatments highlight that each mechanism can be triggered by physical sensations, can have psychological/emotional origins (in the case of an amputation) and could also arise from climate-induced triggers, like temperature or changes in weather. These triggers where investigated by Guinmarra and colleagues [5] who have shown the need for optimising stump and neuoma mechanisms to manage spontaneously triggered phantom phenomena.

III. EMBODIMENT

One area related to cortical reorganisation that appeals to Phantom Limb Pain is that of embodiment. Embodiment has been described as the sense of one's own body [16] which when examining the effects of a surrogate limb virtually on the amputee population is an important area to study. Both visual and multisensory cues can lead to embodiment [17][18]. The use of a prosthesis with some amputees who suffer from Phantom Limb Pain has been shown to lower the perceived levels of phantom limb pain. This is due to the phantom limb embodying the prosthesis [19], the two-way interaction of using the prosthesis and therefore controlling the phantom limb, having an effect on the amputee's existing body schema.

Some amputees who use either standard functional or myoelectric prostheses experience vivid Phantom Limb Phenomena [20] but reduced Phantom Pain [21] [22]. Such results can be explained by the fact that once an amputee engages with the prosthetic limb their proprioception extends to embody the prosthesis [5] [23]. Several strategies have been devised to enhance limb embodiment (magnifying the limb seems to increase pain, whereas minifying the limb seems to reduce pain) with virtual realities with varying degrees of success [24] [25]. Most studies however, have shown more vivid embodiment within amputees whose phantom limb is extended and equates to a sensory map on the amputated stump [25]. Paradigms such as the rubber hand illusion have shown to provide the amputee with a greater sense of embodiment if the amputation is recent [26] with further research showing that tactile feedback enhances the embodiment of a prosthetic limb [27]. It is also suggested that proprioceptive feedback enhances targeted motion within upper limb prosthesis control [28].

IV. TRADITIONAL THERAPY APPROACHES

Many treatments and therapy paradigms have existed to lessen or resolve the acute and chronic pain sufferer's experience. These can be broadly grouped into three main categories: symptom specific pharmacological intervention, tailored psychological, physical and behavioural paradigms and surgical interventions [15]. What this shows is the difficultly faced by phantom limb pain treatment research due to the biological regions affected.

Physical, behavioural and psychological treatments (usually integrated into multimodal rehabilitation paradigms can be further broken down as follows:

- Electrical and sensory stimulation - has traditionally been seen as an effective treatment option for phantom limb pain [29]. However the published findings of this type of intervention yield low-level evidence to support its efficacy [30]. On the other hand, sensory stimulation studies have shown reductions in phantom limb pain and correlated normalisation of cortical reorganisation [31] [32] in combination with other multimodal rehabilitation paradigms mentioned below.
- Psychological intervention - the emotional trauma caused by an amputation can trigger and amplify phantom pain. Cognitive behavioural therapy can be used to treat some elements of the pain along-side other paradigms.
- Visual illusions - therapies such as the mirror box therapy have shown to be efficient at phantom pain management, due to the restoration and manipulation of body representations using mirror visual feedback [33]. A recent study has shown that this type of therapy is most effective with long-term patients with muscular type phantom pain [34].
- Phantom movement therapy - mental imagery has been shown to modify the cortical map associated with the amputated limb and to both relieve [35] and worsen [36] phantom pain experienced by patients. Combinations of various movement therapy paradigms yield greater results [37] however the long term effects of these studies have been called into question.
- Prosthesis use and embodiment - has shown to reduce phantom pain due to embodiment [15] [38] [22]. Prosthesis usage has demonstrated that a patient's sense of proprioception extends to embody their prosthesis, however issues arise in that the phantom limb can differ in size related to the prosthetic limb which causes conflict between the perceived and actual limb [39]. Ehrsson and colleges [25] work suggest that embodiment is strengthen for patients whose phantom extends and can be associated to a sensory map on the stump.

One aspect that is clear from the reviewed literature is the need to combine various paradigms in order to provide more effective means of identifying and managing phantom limb pain. At this point the use of robotic therapy and neurorobotics provides opportunities to explore this multi-modal approach, such as combining movement therapy with prosthesis use.

V. OUR APPROACH

Our approach combines the virtual surrogate residual limb (as used in traditional mirror box therapy) with added haptic feedback using a HapticMaster robot [40]. The work with strokes shows some parallels with upper limb phantom limb pain treatment where similar motor acquisition tasks are used. However seeing the missing limb seems to have the biggest effect on reducing pain in amputees. Building on the work carried out with stroke patients, we combine proprioceptive and kinaesthetic feedback through direct physical contact with a haptic device, and map the information from the device to a virtual representation of the physical limb in an application that maintains challenge and interest to the individual. Which we believe will increase levels of embodiment and thus ensure that the therapy paradigm is more effective than previous work, which has focused purely on visual aspects. As shown in section IV, research has been carried out on primarily the visual system which although have shown positive results often are not as effective on stubborn phantom limb pain. As a result we hypothesise that patients who use the combination of visual (3D life like graphics) and haptic feedback will experience much quicker and longer lasting embodiment and resulting pain relief, as opposed to patients who experience the sole treatment of visual but no haptic feedback. An example of how a patient uses our system can be seen in Figure 1.

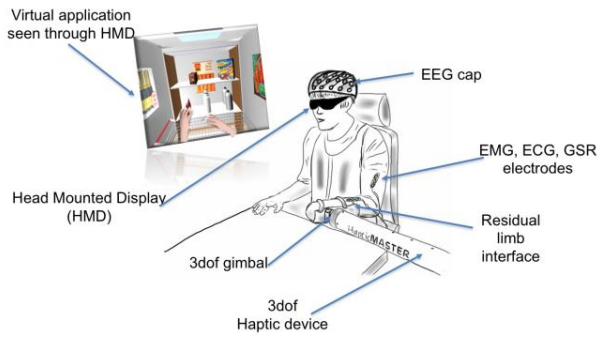

Fig. 1. Illustration showing a user during therapy using the proposed system.

The sensors shown collect both physiological (EMG, GSR, Respiration) and biomechanical (HMD, haptic device, gimbal) data while the user interacts with the system. The patient's residual limb is connected via a custom interface to the haptic device's gimbal that facilitates movements in 6 degrees of freedom (DOF). The system allows for traditional exercises such as the box and blocks test [41] and tasks relating to Activities of Daily Living (ADL) similar to the kettle test [42] to be performed. Grip detection of the residual limb is achieved by the use of EMG pickups. The HMD provides 3D video output to help immerse the patient in the exercises (first person view), an ability that strengthens embodiment and can lead to successful rehabilitation paradigms [11] [43] [44].

VI. SYSTEM ARCHITECURE

The system architecture (Fig. 2) is represented as a closed-loop system where the loop is closed around certain human responses while interacting with a virtual task. Such components are characterised by four main modules.

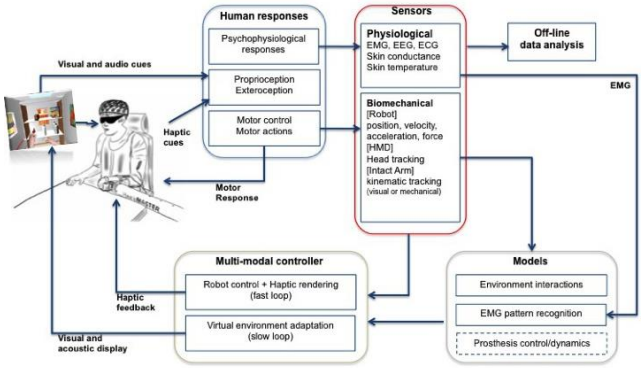

Fig. 2. AMPSIM system architecture overview

A. Human Responses

The human responses represent the user interaction with the system, which takes the various human input from responses to visual, audio and haptic cues from the exercises and results in output from these cues. The resulting data that is logged via the sensors is fed back into the system (via the controllers). These human responses to events during the exercises are logged into a database and are used as event triggers in the offline analysis of the data. A range of haptic effects can be applied to the system such as springs, dampers, biasforces and shakers. The HapticMaster API can also render a range of simple haptic primitives such as blocks, spheres, flatplanes, cylinders and torus, which is broad enough to render everyday objects such as, cans, books, tables etc needed for ADL tasks. The maximum force the HapticMaster can exert is 250N, nominal 100N, which allows the system to provide realistic forces to allow differentiation between, objects such as a solid table and a plastic bottle for example.

B. Sensors

Physiological sensor information is used to quantify psychophysiological responses to the audio-visual and haptic cues provided by the system. Perception of the environment (and from the haptic cues) will invoke proprioceptive and exteroceptive user responses that will result in motor actions and a subsequent response (e.g. movement of the limb, feeling the weight of an object). Possible motor control actions are picked up by a range of different biomechanical sensors present in the robot, by the Oculus Rift [45] HMD and kinematic tracking of the intact/residual limb via AR markers and inverse kinematics. The kinematic tracking of the intact limb is provided via the three gears system [46] which uses a 3D camera pointed downwards to the patient work space to detect and process the intact arm's hand and subsequent hand/finger position and gesture tracking. This allows the system to accurately track and display the intact limb thus delivering a more immersive experience. With

EMG sensors detecting grasp/release with the amputated limb to allow a greater number of tasks, and also to enhance embodiment. This part of the system acts as the throughput from the human responses module and other joining modules.

C. Models

Representations of the environment interactions are used to define behaviour and interaction paradigms upon a certain input (e.g. object to change colour when touched), whereas simple EMG pattern recognition helps identifying motor intention (e.g. move limb, open hand). OpenVibe [47] is used to collect and classify data from the EMG pickups sent via VRPN [48] into the system as well as the database.

D. Multi-modal Controller

The control and interaction loops close around a multi-modal controller consisting of a fast loop (control and haptic rendering) for haptic feedback that runs at an update rate of 2500Hz and a slow loop (virtual environment adaptation) for audio-visual feedback. The virtual environment in which the exercises take place is located in this module, along with the haptic effects, which change the parameters of the environment. The workspace of the HapticMaster is 80.10^{-3} [m^3] which is suitable for simple tabletop ADL tasks.

E. Typical usage

Figure 3 shows the system prototyped, which uses a single Primesense camera for the three gears system and the Oculus Rift to provide a more immersive experience for the user. The screenshots from the right hand side of Figure 3 also show an example of the exercises developed (a simple pick and place exercise). The environment is created using Vizard [48] from WorldViz running on a single windows 7 workstation.

Fig. 3. Healthy user interacting with a pick a place exercise during system development in the lab. Left images show the user wearing a HMD with limb connected to the haptic device. Right images show an example of a virtual exercise.

VII. Future Work

Short to long term clinical trials with the system are underway using two groups of patients. A VR only group and a VR with Haptics group to contrast the results between the two to examine the effectiveness of haptics applied to patients with Phantom Limb Pain. We believe that the latter group will experience a stronger and quicker decrease of perceived pain compared to the former group. In the future we would like to expand the length of the clinical tests as well as examining the cortical reorganisation and other neurological paradigms. Previous studies have highlighted the need for more in-depth examination of neurological effects using robotic based therapy, in order to gain a deeper understanding of Phantom Limb Pain overall. Table 2 highlights how the project can improve on these areas.

Conclusions	Addressed by AMPSIM
Posture affects kinematic recordings of the residual limb[49].	Both the residual and intact limbs position and orientation are tracked using a hybrid kinematic and visual tracking approach.
Long(er) term intervention is required. Most studies consist of short term interventions (a week or two maximum)[15].	The AMPSIM study consists of a two-phase clinical study where the intervention phase will be carried out over a three-week duration and a three-week follow-up to evaluate retention gains.
High quality 3D environments and textures (via a high quality display) are needed to provide a totally immersive experience to the user [50].	The method of display used within AMPSIM not only has very high quality video output but in 3D providing a fully immersive training paradigm. The 3D element is a necessity due to depth perception whilst performing reach and grasp movements.
The majority of current systems do not provide haptic feedback [51], [52], [50].	In order to aid immersion and strengthen embodiment the main interface that connects the user is the haptic device and provides force feedback while interacting with virtual objects.
Often studies focus more on verbal feedback (pain questionnaires) about the effect of pain and do not examine the real-time biological effects of pain [51],[52], [50].	Real time recordings taken during the exercises will aid off line data analysis, with the psychophysiological sensors acting as biomarkers for the recordings. These measures are used in conjunction with standardised pain questionnaires (e.g. McGill pain questionnaire).
The use of multiple psychophysiological sensors are essential to detect cognitive stress during clinical studies [53] [54].	GSR readings have been shown to be a reliable indicator of cognitive stress[55], [56] however as [53], [54] have shown multiple sensors are needed to detect cognitive changes. As well as GSR the AMPSIM clinical studies will also use a respiration sensor to measure changes in breathing.

Table. 2. How the project will address current issues with existing robotic rehabilitation paradigms.

VIII. CONCLUSION

This paper has introduced a system developed to examine the effectiveness of haptic therapies on relieving Phantom Limb Pain in amputees compared to current therapies. We believe that by combining several technologies such as immersive 3D HMD's, accurate intact hand tracking and gesture recognition added to the already proven benefits of robotic therapies, will yield positive results. The complex nature of Phantom Limb Pain has lead to many potential treatments all with various levels of results. The key to a successful treatment paradigm points to a multi modal approach which due to cost or lack of technological advancements have eluded previous treatment success rates. The level of immersive therapy and its subsequent results poses more questions when transferring such paradigms to other movement-based treatments. However more long term studies are required with more emphasis on how these paradigms affect the patient's neurological state both long term.

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Robotic Therapy for Phantom Limb Pain in Upper Limb Amputees

Peter W Snow *Member, IEEE,* Imad Sedki, Marco Sinisi and Rui C.V. Loureiro *Member, IEEE*

***Abstract*— Advances associated in terms of cost and quality in virtual reality have brought new paradigms to help with rehabilitation in a vast range of areas. Previous systems have focused on visual based only paradigms with varied results. The system described in this paper draw not only from visual based approaches but also adding elements of haptics to increase the level of immersion but in combination also invoke the sense of agency in patients with phantom limb pain. This paper presents three case studies of an on-going clinical study. The initial results suggest an increased sense of embodiment of the virtual limb promotes a decrease in perceived levels of pain. The results strengthen the view that the cortical map does not fully "disappear" yet lays dormant.**

I. Introduction

The decision as to whether to attempt limb salvage or an amputation is difficult but in either case there are subsequent problems with rehabilitation including phantom pain and limb non-use[1]. Phantom limb phenomenon affects a large percentage of amputees (50-80%) and results in feeling body parts that are no longer there[2]. Amputated limbs can ache, itch, burn, feel dry or wet, tense, locked or stuck, or even feel they are moving[2], [3].

The effects of Phantom Limb Pain (PLP) can worsen due to anxiety/stress and other factors[2]. Not only does this affect the individual's mental wellbeing (coping with the psychological trauma associated with the limb loss) but also their physical state (imposed by the chronic pain effects) and the rehabilitation outcome[4]. Regional rehabilitation units, Defence Medical Rehabilitation Centres and NHS rehabilitation centres are posed with diverse challenges as the individual experiences emotional discomfort in addition to psychological trauma, reduced mobility and Phantom Limb Pain[5].

One treatment option available is mirror box therapy, which has been shown to have an effect in some amputees in reducing PLP[6], [7], however this tends to result in short term relive[8], [9]. It is believed this is due to the amputee embodying the visual mirror image of their intact limb where their amputated limb is located. One method of enhancing embodiment of a visual surrogate is to employ tactile feedback which has been shown to reinforce embodiment of a visual image within both the amputated and non-amputated population[10]-[12] and thus more longer periods of relive. Which has lead to research in using TMS to provide targeted feedback back to the CNS to allow amputees to feel objects they are holding onto with their prosthetic limb[13].

Our on-going clinical pilot study taking place at the Royal National Orthopedic Hospital, Stanmore and other partner sites, aims to establish a more solid scientific framework for advancing the knowledge of haptic interaction in the treatment of Phantom Limb Pain and its outcome will be used to inform a future phase II trial to quantify the new approach in terms of cost benefit and therapeutic practice. In this paper we present a robotic system that facilitates retraining of simple manipulation tasks by amputees and initial results from our on-going clinical trial.

II. Methodology

A. The system

Motor tasks are performed using an immersive haptic sensorimotor training system (Fig. 1) that provides, direct physical contact to a haptic robot, mapping of the information from the robot to the virtual representation of the physical limb, and an application that maintains challenge and interest to the individual. Based on these elements, the system acquires EMG commands, residual limb kinematics and displays the combined residual limb movements in a virtual reality environment that includes force-based interactions with virtual objects. Visualisation is provided via a Head Mounted Display so as to facilitate first-person view of the virtual environment and embodiment of the residual limb with the virtual representation[14], [15]. The Unreal Engine 4 is used to render the exercises together with custom software that synchronises the control loops and communication with the different subsystems.

The participant is connected via a residual limb interface (gimbal) to the haptic robot (HapticMaster), which provides limb tracking in 6-dof (position and orientation) and force feedback in 3-dof. A Primesense camera with supplemental Nimble [16] camera hand tracking system is placed on the table via a flexible stand to track the participant's intact hand. The haptic robot has two purposes; 1) to support and track the amputated limb's movement and 2) to provide haptic feedback. The residual limb interface can be customised to fit different stump sizes.

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Imad Sedki and Marco Sinisi are with the Prosthetic Unit and Peripheral Nerve Injury Unit (respectively) at the Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, HA7 4LP, UK

Rui C.V. Loureiro with the Aspire Centre for Rehabilitation Engineering and Assistive Technology, University College London, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, London, HA7 4LP, UK Contact: r.c.v.loureiro@ieee.org

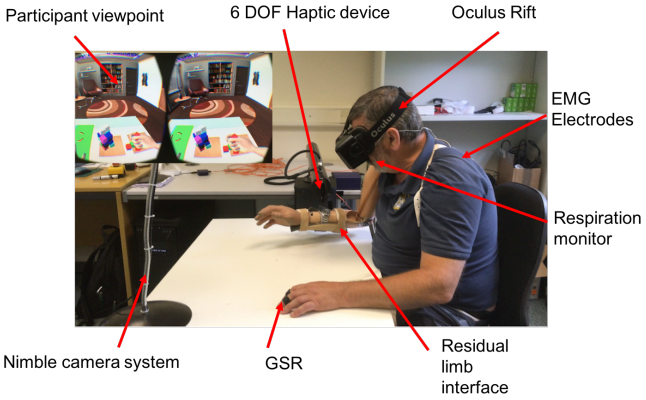

Fig.1 Typical set up of the system in a right handed configuration showing a participant connected to the 6dof robot. Top left image shows the participant's view of an exercise.

Position and orientation data from the gimbal of the haptic robot and Nimble camera is fed into a custom made inverse kinematic solver which produces the correct anatomic position and orientation for a virtual avatar upper limb being controlled by the participant. The benefit of using a pure immersive VR approach is that scaling up the movement of the virtual limb being controlled via the participant becomes straightforward.

Haptic effects are applied in such way to simulate different object weight properties, collisions on impact with other objects and textures of various materials that a participant could interact with. The haptic layer of the system is separate from the visual layer with communication between a custom made HapticMaster plugin in Unreal Engine 4 and a haptics server via TCP protocol.

The Oculus Rift HMD (DK2 version) is used to provide a stereoscopic first person view of the virtual environment collocated with an avatar head and body position. The Nimble camera hand tracking system tracks the participant's intact hand not connected to the haptic robot. Due to the unilateral exercises, the intact limb used to start the exercises and to provide the participant with control over the exercises by placing the virtual intact limb onto a green rectangle placed on a table in the virtually environment. The decision to use this type of virtual control over a more physical control was due to efforts ensuring that the immersion of the exercises was not broken during the sessions.

EMG sensors are placed on participant's suitable residual muscles. A training session is carried out to extract and classify muscle features to be mapped to a binary open/close of the virtual hand of the avatar. A TMSi Porti amplifier is used to collect all physiological sensors at 1024Hz. In order to identify grasp and release training data is classified using OpenVibe[17]; a LDA classifier is used in a custom made OpenVibe script which takes all the physiological data channels, correctly segregating the channels (EMG, Galvanic Skin Response and respiration) before sending the raw and classified data to the Unreal Engine 4 system via the VRPN protocol[18] and a small python script. The VRPN signal sent to Unreal Engine 4 is only a binary value, however different kinds of grasp can be selected for each exercise.

Other physiological sensors such as GSR sensors placed on the fingers of the intact hand and a respiration sensor placed underneath the nose with probes in front of the mouth and in the nostrils, are used to gather the secondary measures, following the same data flow as mentioned above.

The system has been designed to log all data per exercise as csv files to be preprocessed and analysed at a further date within the correct participant information automatically via a drop down menu filled in at the start of the session.

The system acts as a decoupled version of the mirror box therapy adding in the sense of agency in that the participant is not only seeing (via the Oculus Rift) the correct position and orientation that their phantom limb (via the virtual limb), but that they are controlling the reaching and grasping movements (via the EMG electrodes placed within the residual muscles of the amputated limb) and physically interacting with the virtual objects.

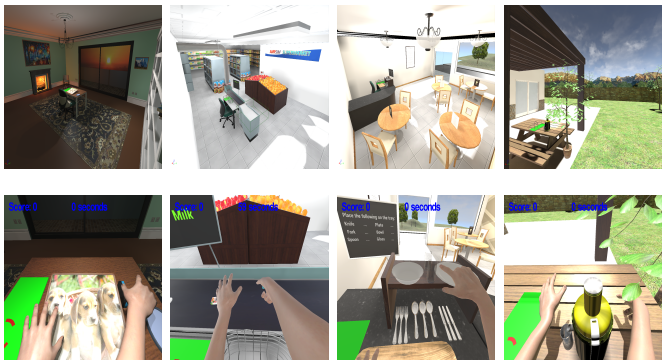

Fig.2 Top row of images shows 4 exercise areas with the bottom images showing the participant view point of those exercises.

Several ADL exercises have been developed (Fig.2) for the participant to undertake during the therapy sessions. These include:

1. An exercise inspired by the blocks and box test.
2. A cleaning exercise in which the participant is tasked with grasping an eraser and using it to clean a painting filled with dust.
3. A shopping exercise in which the virtual avatar is placed in front of a conveyer belt with moving items. The task involves the participant reaching to grasp objects and placing them in a basket in front of the virtual avatar.
4. A restaurant scene in which the participant picks and places objects such as dishes, glasses, forks and knives onto a tray.
5. Juice making task carried out by picking fruit from a tree and placing the fruit into a juicer.

C. Clinical Study

1) Methods

A total of 20 participants are being recruited to the study. Participants are placed into one of two groups, a control group (visual surrogate for the missing limb without the force feedback) and an experimental group (visual surrogate for the missing limb with force feedback). The study was approved by the NHS ethical committee and is on the NIHR portfolio. This paper presents the initial results obtained with three case studies recruited to the on-going study for the RNOH Stanmore cohort (Mean age – 50.3 Mean time since amputation – 12.3 years, SD 21.54) who have fully completed the robotic intervention and follow up assessments. An overview of the participants can be found in (Table. 1).

2) Participants

Participant ID	Gender	Age	Amputation Side	Amputation Level	Time since Amputation	Prosthesis Used	Onset PLP	Medication	Group
RNOH2	Male	58	Right	Transhumeral	30 years	Cosmetic	Since operation	Yes	VR
RNOH3	Male	26	Right	Transhumeral	1 year	Cosmetic	6-7 months post operation	No	VR & Haptics
RNOH4	Male	67	Left	Transhumeral	6 years	None	Since operation	Yes	VR & Haptics

Table 1. Participant Summary

RNOH2 is a 58-year-old male assigned to the control group who via an accident lost his right arm and leg over 30 years ago. Immediately after the accident he had his right arm amputated above the elbow. He experienced PLP straight after the operation and had been on medication (Pregabalin & Gabapentin) ever since. This participant has been a prosthesis user since the operation (dominant hand was his left side) and has used the same body powered prosthesis since his operation.

RNOH3 is a 26-year-old male assigned to the experimental group who lost his right arm (also his dominant side) via a motorbike accident over 2 years ago. An above the elbow amputee in which the onset of PLP started a year after the amputation. This participant did not take any medication for the pain and has been using a cosmetic prosthesis since the amputation.

RNOH4 is a 67-year-old male above elbow amputee assigned to the experimental group who lost his left arm via an accident 10 years ago. Onset of PLP was instantly post amputation and he has been on medication for the pain ever since (Pregabalin & Gabapentin). This participant is a non prosthesis user, however due to the level of amputation and the set up of the equipment a cosmetic prosthesis was made to be worn for the duration of sessions. His dominant side is his right side.

3) Measures

Physiological sensor information is used to quantify psychophysiological responses to the audio-visual and haptic cues provided by the system. Perception of the environment (and from the haptic cues) invoke proprioceptive and exteroceptive user responses that result in motor actions and a subsequent response (e.g. movement of the limb, feeling the weight of an object). Possible motor control actions are picked up by a range of different biomechanical sensors (present in the haptic device), by the HMD (head tracking) and kinematic tracking of the residual (and intact) limb. A series of outcome measures assessing changes in reported pain, embodiment, psychophysiological responses, muscle activation, kinematics features and qualitative information in the form of a diary, are used to quantify therapy effectiveness.

In this paper we report on the perceived pain and embodiment measures:

- McGill pain (short) questionnaire: was used to measure perceived levels of pain experienced by the participant taken at the beginning of the study, at the end of each therapy session and at a follow up session.
- Botvinick's embodiment questionnaire[19]: was used to measure perceived levels of embodiment (limb ownership) that the participant may experience, which is taken at the end of each session.
- Proprioceptive drift estimation: was used to measure the perceived level of embodiment before and after the intervention session. This measure consists of taking the distance the participant perceives their limb has moved. Two measurements (participant points to where they think the center of their hand is) are taken one before and another after the exposed immersion (before/after each session). The difference is produced and used as the measure of proprioceptive drift.
- Pain diary: participants were asked to keep a pain diary for the length of the study until final follow up.

4) Data Collection & Analysis

Both internal UE4 data (information about the virtual avatar and other level specific objects) along with external data such as raw EMG data and kinematic/kinetic data from the HapticMaster are synchronised and saved in a text file for offline processing.

It is anticipated that if the hypothesis is supported, significant larger effects (higher pain reduction and increased embodiment levels) will be observed on the VR + Haptics group when compared to the VR only group. This initial analysis will also allow us to observe any temporal effects on pain and embodiment. We estimate a higher temporal effect (e.g. steeper slopes earlier) with the VR + Haptics group.
We acknowledge that the effect of novelty (just the fact of someone being involved in the trial) might have an impact on the results.

E Study Timeline

Participants had an initial meeting (Fig.3) in which the study was further explained and consent was taken. This was followed later by a preparation session used to set up the sensors and conduct EMG pattern recognition for each participant. An initial pain questionnaire was also taken along with allocation of a pain diary.

The subsequent three weeks involved nine sessions (1 hour each) spread evenly. The proprioceptive drift is taken before and after the session, short McGill and Embodiment questionnaires are taken at the end and all sensor/kimematic/kinectic data is automatically collected during the session. For each session one hour is used for performing the exercises with the robot.

After three weeks of intervention a post intervention period of three weeks followed in which no further intervention with the robot took place.

Finally, two follow up sessions six and twelve weeks since study start are conducted where a short interview were conducted along with short McGill and proprioceptive drift measurements.

Fig.3 Flowchart showing the study time line.

III. Results

A. Overview

Overall no negative side effects in terms of pain are reported. Further analysis is required on the kinematic data, therefore the focus will turn to the McGill Pain (supplemented by the participant's pain diary) & our modified embodiment questionnaire along with the proprioceptive drift measurements. The McGill pain questionnaire is scored from 0-5 (0 being no pain). The embodiment questionnaire uses a likert-type scale from 1 (strong disagree) to 7 (strongly agree). Question 3 will be presented only due to the general nature of the question "I felt as if the virtual limb were my (real) limb.". In terms of proprioceptive drift the majority of the reported participants in this paper show a trend of decreasing error in distance taken from post intervention measurement minus pre intervention measurement. In contrast with the majority of reported proprioceptive drift measurements in the literature, the results presented in this paper take into consideration both the X & Y coordinates not just a single axis. This was done to make the results as accurate as possible.

B. Case study I - RNOH2

As shown (Fig.4), for RNOH2 there does seem to be an initial correlation in terms of increased embodiment and a decreased level of reported pain from sessions 1-6. With a one point score increase from session 6 to session 9 however ending the sessions with less pain than the baseline pain score. Although there is an increase in pain between the first and second follow up sessions the participant noted that other factors have contributed to this increase. The participant reported in their pain diary that for a week and a half from the end of the sessions there was little or no pain (score < 1). This participant was placed within the control group (VR only) and uses prosthesis. Interestingly the participant noted that it took some time for him to believe that it was himself controlling and opening and closing of the virtual hand via EMG, this could explain the jump in embodiment towards the 4th session. Examining RNOH2's pain diary the levels of pain during the intervention period of 3 weeks during the intervention the average pain recorded by the participant was 1.9/5 (Standard deviation 0.98) whilst post intervention the average pain recorded was 2.9/5 (Standard deviation 1.27) .

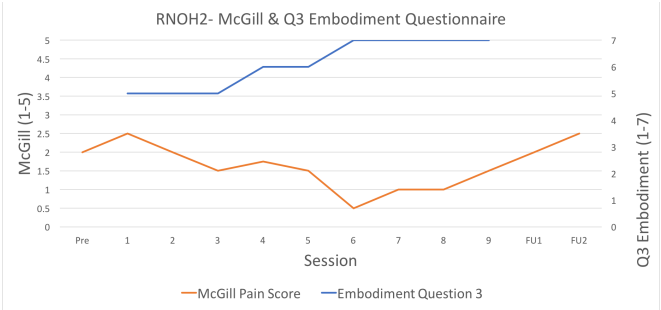

Fig.4 Plot showing both the McGill pain score in orange (0-5) and question 3 of the embodiment questionnaire in blue (1-7) from baseline through to the 2nd follow up session for participant RNOH2.

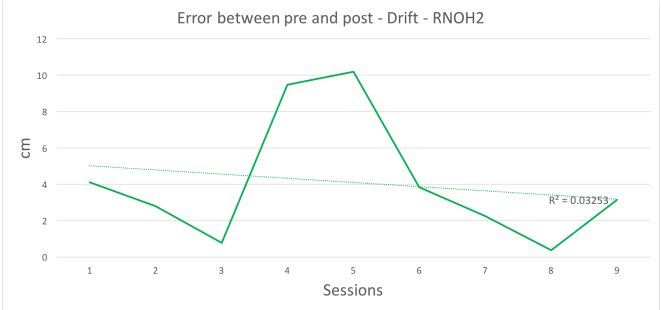

Fig.5 Plot showing the error in cm between drift measurements taken pre and post session during the 9 intervention sessions for participant RNOH2.

RNOH2's proprioceptive drift error (Fig.5) does generally suggest a decrease (linear $R^2 = 0.03253$) despite an approx. 9cm jump increase from sessions 3 to 4. However, this could be explained due to the fact that 3 sessions were scheduled a week with a 4 day gap between the 3rd and 4th sessions for this participant. With most of the error being 4cm or less between the start and end of the intervention sessions.

C. Case study II - RNOH3

RNOH3 who is a prosthesis user was placed in the experimental group (VR + Haptics) out of the three participants reported in this paper experienced the best outcome in terms of pain levels. As shown by (Fig.6), by the 3rd session there was no pain reported even at the final follow up session. Despite the elimination of pain during the intervention there was 12 self reported instances of pain (average of 2/5 Standard deviation 1.42) written in the pain diary post intervention.

However these episodes of pain were reported to last seconds to the maximum of 10 mins. The participant reported that he was able to get the pain to go away quickly employing tactics such as distraction or imagining performing the one of the exercises during the intervention. The participant was a recent amputee (approx. 1 year), which might account for the effectiveness of the intervention. Despite a dip in the level of embodiment in session 2 there seems to be a strong link between embodiment and the perceived levels of pain reported.

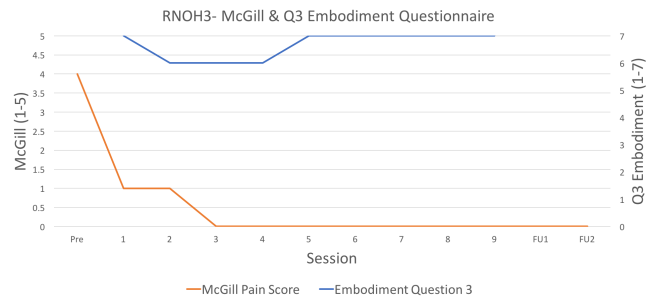

Fig.6 McGill score and embodiment question graph for participant RNOH3.

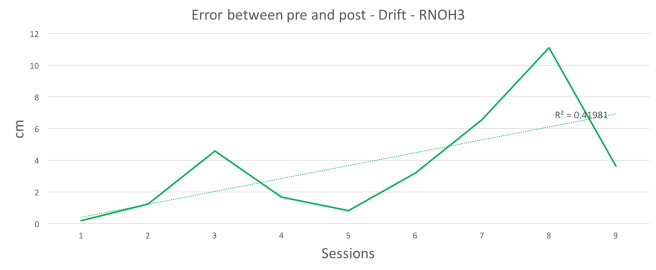

Fig.7 Drift error graph for participant RNOH3.

RNOH3's proprioceptive drift error (Fig.7) remained fairly low to session 6 (similarly to RNOH2's < 4cm, average 1.9cm error) Standard deviation 4.56 with an 4.54cm increase in error during sessions 7 and 8. One possible reason for this could be due to the fact that sessions 6 and 7 were held on the same day with session 8 being held the day after, fatigue may be behind this increase in error despite the embodiment questionnaire suggesting otherwise. This resulted in an increase trend (linear $R^2 = 0.41981$) in error during the sessions.

D. Case study III - RNOH4

RNOH4 who did not use a prosthesis and had one made for the clinical study, and was also placed on the experimental group (VR + Haptics). Interestingly, unlike the two previous case studies presented in this paper there is little to no link between embodiment and reported levels of perceived pain (Fig.8). The lack of embodiment and fluctuation of pain levels might be attributed to the participant's non-usage of a prosthetic limb. Despite this fluctuation we also suggest that a longer period of intervention might raise the level of embodiment and thus lower the perceived levels of pain. As noted in the RNOH4's pain diary, reduced pain levels in general were reported from just before the 7th session. This further reinforces our suggestion that longer intervention for this particular participant would be beneficial. In addition, we also extracted from the pain diary the average pain during intervention (2.9/5, Standard deviation) and post intervention (2.8/5 Standard deviation) but also an average decrease in the time the pain was present as recorded by the participant; approx. 20 minutes per day on average during the intervention period vs. approx. 9 minutes per day on average post intervention, a decrease of approx. 11 minutes.

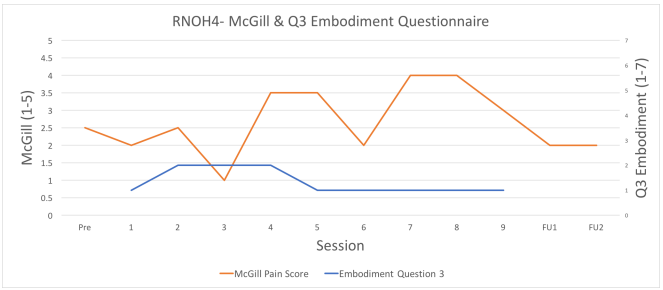

Fig.8 McGill *score and embodiment question graph for participant RNOH4.*

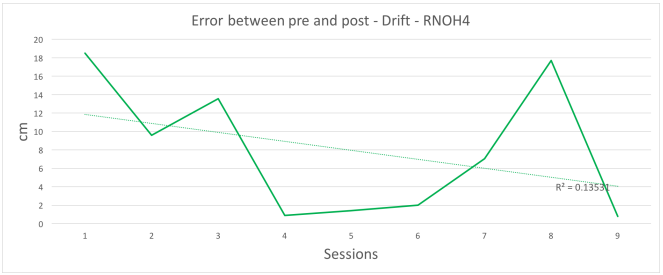

Fig.9 Drift error graph for participant RNOH4.

Interestingly although RNOH4 did not show much embodiment via the embodiment questionnaire the proprioceptive drift error results (Fig.9) do generally tell another story. That is, a sharp decrease can be observed up to session 4, with only a minor increase between sessions 4 and 6. However, a 15.71cm increase in error between sessions 6 and 8 followed by a 16.92 decrease in error for the final session can be noted. With this taken into consideration a decreasing trend line (linear $R^2 = 0.13531$). Although the

drift error does not correspond to the qualitative embodiment measure it does explain the reduced level of perceived pain mentioned in this participant's pain diary.

IV. Conclusion

This paper has outlined our novel system in combining VR and haptics to aid in the reduction of Phantom Limb Pain. Initial results presented with the reported three case studies seem to support our design goals, in that the system is used to strengthen the participants' embodiment of a virtual limb by exposing the sense of agency coupled with haptic effects in lowering perceived levels of pain. The link between embodiment and pain for the majority of these cases does suggest a correlation.

The initial results seem to suggest lower levels of perceived pain as a result of exposure to the intervention. Although no firm conclusion can be drawn from three case studies, it appears that the sense of agency rather than embodiment could possibly be a larger factor in pain reduction than thought before.

Based on our initial results, one trend seems to be emerging – amputees who are either recent amputees (prosthesis or non prosthesis users) or long-term amputees who are regular prosthesis users, might experience larger pain reduction benefits.

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Immersive Robotic Therapy for the Treatment of Brachial Plexus Pain

Peter W. Snow [1,2,4,*], **Dace Dimante** [4,5], **Marco Sinisi** [3], **Tom Quick** [3], **Richard Comley** [6] **and Rui C.V. Loureiro** [1,2,4,*]

[1] *Aspire Centre for Rehabilitation Engineering and Assistive Technology, University College London, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, London, HA7 4LP, UK*
[2] *Wellcome / EPSRC Centre for Interventional and Surgical Sciences (WEISS), University College London, UK*
[3] *Peripheral Nerve Injury Unit at the Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, HA7 4LP, UK*
[4] *National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK*
[5] *Riga Stradins University,Dzirciema iela 16, Kurzemes rajons, Riga, LV-1007, Latvia*
[6] *Middlesex University, The Burroughs, Hendon, London NW4 4BT, UK*

Correspondence*:
Peter Snow/Rui Loureiro
p.snow/r.loureiro@ucl.ac.uk

ABSTRACT

Brachial Plexus injuries are complex in nature caused in large by high impact traffic accidents which can lead to additional complications such as Complex Regional Pain Syndrome and even lead to amputation or the need for further surgical intervention. Treatment options to help repair the brachial plexus initially involve surgical intervention and post surgery rehabilitation with medication to help with ongoing pain. Pain treatments used for these types of injuries are limited and differ in effectiveness. Paradigms utilising multimodal systems such as the one described in this paper could yield results that are non invasive and provide better rehabilitation outcomes for the sufferers. This paper examines a sub population of participants with brachial plexus injuries from the Royal National Orthopaedic Hospital, Stanmore who took part in a larger clinical study on Phantom Limb Pain in upper limb amputees.

Keywords: Rehabilitation, Pain, Brachial Plexus, Robotics, Haptics, Virtual Reality

1 INTRODUCTION

1.1 Brachial Plexus Injuries

Brachial plexus injury is devastating peripheral nerve trauma often as a result of vehicle (mainly motorcycle) accidents (Nagano, 1998). The majority of these injuries occur in high velocity collisions in which the neck and head experience enough impact force and traction for the nerve roots to break or tear away from the spinal cord. The level of injury is factored through the specific roots and degree of injury to each root. The effects of a brachial plexus injury usually lead to paralysis, loss of sensation, and

debilitating, often intractable pain, therefor causing severe physical, psychological and socioeconomic disability.

The degree of disability is determined by the extent of injury to the nerve roots. Severely limited range of motion or even complete loss of function of affected arm and/or hand makes rehabilitation extremely challenging.

Treatment is multidisciplinary, longitudinal in nature and often involves primary explorative +/- reconstructive and further staging of secondary, even tertiary surgical procedures. This results in high cost of treatment and rehabilitation in this population group. Not to mention, the cost is further increased by the gross number of people not being able to rehabilitate and reach reasonable quality of life due to severe pain in the affected limb.

1.2 Pain

Brachial plexus injuries commonly result in pain. It is reported in 67% to 78% of patients (Treede et al., 2008)(Teixeira et al., 2015) with high prevalence of neuropathic pain, reported in up to 95%., especially in cases of nerve root avulsion (JL et al., 2008)(Ciaramitaro et al., 2010). In brachial plexus injury pain poses an additional negative factor further reducing quality of life (Teixeira et al., 2015). Pain in these cases is multifactorial and difficult to manage. There are mainly two groups of pain - nociceptive and neuropathic. The former is related to direct musculoskeletal and soft tissue trauma resulting in a complex cascade of inflammatory reaction. The latter is associated with dysfunction of peripheral and, in a later stage, central nervous system (Treede et al., 2008)(Kennedy, 2007). These central neurophysiological and molecular changes are responsible for refractory neuropathic pain (Macyszyn et al., 2011)(Yoshikawa et al., 2012) and a phenomenon known as phantom limb pain. Therefore, the pain management is complex and sometimes ineffective. Additional injuries such as amputation at the time of brachial plexus injury or at a later time, when amputation is a choice of treatment to alleviate mechanical strain of non-functional extremity, can present even more challenges in pain management.

1.3 Treatment Options

There are two major treatment options - conservative (pharmacological) and surgical. Conservative management aims to maintain as much function and range of movement as possible in the affected limb via strengthening existing functioning muscles whilst providing pain relief. Additionally, combined pharmacological treatment is provided to further manage the pain. Surgical interventions on the other hand aim to restore function of the injured arm which can in some cases reduce the pain (Ciaramitaro et al., 2010).

1.3.1 Conservative

This method is a combination of pharmacology, physiotherapy and rehabilitation, and can include biofeedback, percutaneous nerve stimulation, hypnosis and similar procedures all aimed to strengthen residual function and reduce pain. NSAIDs and opioids reduce nociceptive pain, whereas neuropathic and phantom limb pain is harder to tackle and antiepileptics and antidepressants can be used. Moreover, only 30% of people with brachial plexus injury and neuropathic pain will have significant reduction in pain with drugs such as gabapentin, etc (Ciaramitaro et al., 2010).

1.3.2 Surgical

There is a variety of surgical techniques used to treat brachial plexus injury. These techniques aim to restore or improve the function of affected limb as well as reduce pain (Teixeira et al., 2015). Early exploration, repair, if possible, and nerve transfers have proven to be successful in improving functionality of the limb and recovery. Decompression of the lesion allows nerve recovery and improves pain. Even slight improvement in limb movement may reduce pain.

However, cases exist in which surgery alone, and even paired with conservative management, does not provide acceptable levels of pain relief, leading to new treatment options being sought for to help the most severe cases.

With incidences of traumatic brachial plexus injuries increasing coupled with the rehabilitation demands on already overloaded services to which incorrect efforts could lead to massive decreases in terms of quality of life for sufferers.

Although surgical interventions are continually improving in techniques and outcomes, functionality still varies. Partly due to the complexities of such injuries, the knock-on effects can factor into the patient's ability to partake in rehabilitation. Therefore, a need to allow those who are most at risk due to severe lack of movement to take part in rehabilitation not only for function but also to manage pain is required. The following sections of this paper detail an immersive virtual reality and haptic robotics system that allows individuals with traumatic brachial plexus injuries with severely limited range of movement, to undertake the same rehabilitation exercises as those with normal range of movement.

2 METHODOLOGY

2.1 The System

Participants performed a number of motor tasks using an virtually immersive and haptic sensorimotor training system developed for the AMPSIM project (Snow et al., 2017)(Snow et al., 2014) (Figure 1). The system provides 1) direct physical contact to a haptic robot (in this case a HapticMASTER), 2) mapping movement information from the robot to the virtual avatar and 3) interactive applications aiming to challenge the participants. Based on these factors, the system acquires EMG commands via sEMG electrodes, residual limb kinematics from the robot and displays the combined information within a virtual reality environment which, includes force-based interactions such as weight, collisions and textures with virtual objects. Visualisation of this virtual environment is via a Head Mounted Display (Oculus Rift CV1) which provides a first-person view of the environment, avatar and subsequent embodiment of the residual limb. Unreal Engine 4 was used as the primary engine used to render the exercises and avatar along with custom software that synchronises the control loops mainly via the engine and HapticMASTER server along with communication with the different subsystems which make up the whole system.

Participants are connected to the robot via a residual limb interface (gimbal), which provides limb tracking in 6-DOF (position and orientation) along with force feedback in 3-DOF. An Oculus Touch controller is attached to the participant's intact limb. This is to facilitate 6-DOF tracking of the intact limb in relation to the Oculus Rift headset. This set up allows easy tracking of both limbs in left and right sided amputation configuration with minimal physical changes between the two sides.

The position and orientation data from the HapticMASTER via the gimbal and the Oculus Touch controller is fed into a custom inverse kinematic solver within UE4, which results in correct anatomic position and orientation of the virtual limbs of the avatar being controlled by the participant. This approach

Figure 1. Participant using the AMPSIM system. Showing the HapticMASTER robot, Oculus Rift and experimenter's screen.

of using an immersive VR paradigm has benefits, in custom scaling movements easily of the virtual limb being controlled via the participant. This is crucial when applied to brachial plexus injuries. Due to the plugin used by Unreal Engine to communicate with the Haptic Master; scaling movements in each individual axis (X,Y and Z) can be achieved with different values for separate axes. These scalar values are also taken into consideration when applying forces back to the Haptic Master. This is key in providing the means for brachial plexus participants to achieve the same "artificial" range of motion as a participant with better range of motion.

Haptic effects are used to to simulate weight, collisions and texture properties applied to individual objects. This is achieved with changing the for example friction parameters, external and internal material properties to produce suitable haptic feedback for a given object. This haptic layer of the system is completely separate from the visual layer within UE4, with communication between UE4 and the haptics server achieved via a custom written plug in using the TCP protocol. This has the added benefit that multiple robots can be used within the system.

The Oculus Rift HMD (CV1 version) is used as the primary HMD to allow the participants to have a stereoscopic first person view of the virtual environment collocated correctly at the virtual avatar's head position. This is achieved via the Oculus Rift's external tracking camera calibrated to correctly place the participant's view point virtually using the physical position and orientation. Using the Oculus Touch controller add on to the Oculus system allows tracking of the participant's intact hand not connected to the robot.

sEMG sensors are placed on participant's residual muscles depending on the participant's level of amputation and requirements. A training session is carried out before the first session and when required during the study to extract and classify the muscle features which are to be mapped to a binary open/close of the virtual hand within UE4. A TMSi Porti amplifier with 32 channels was used to collect all physiological

data at 1024Hz. OpenVibe (Renard et al., 2010) an open source BCI acquisition server and designer was used to identify grasp and release training data along with classifying the data (using an LDA classifier)to be used online within the sessions; This allows all the physiological data channels, correctly segregating the channels before sending the raw and classified data to the Unreal Engine 4 system via the VRPN protocol (Taylor II et al., 2001).

All data produced from the exercise in UE4 and from OpenVibe are saved automatically per exercise as csv files which are then preprocessed and analysed offline.

The system has a simple task, to act as a decoupled version of the mirror box therapy. The additional haptic feedback facilitates the sense of agency and embodiment, in that the participant is not only seeing (via the HMD) the corrected position and orientation that their missing limb should be in (via the virtual limb), but also that they have a sense of controlling this limb via reaching and grasping movements (via the EMG electrodes and robot) and physically interacting with the virtual objects. The use of the robot allows those who's range of movement might be impaired to experience the benefits of believing that they are correctly reaching objects beyond their physical reach due to the immersive properties and correct individual scaling to allow them to achieve full control.

The combinations of these technologies mentioned above and shown in Figure 2); Haptics (providing force feedback) allows participants to feel and interact with virtual objects with associated physical properties attributed to the objects and environment, along with mapping physical movements virtually. Classified EMG (providing control along with enabling the sense of agency) facilities fine motor control of the hand to interact with the environment. Lastly Virtual Reality (providing stereoscopic output for the participant thus strengthening the visual surrogate of the avatar) allows participants to feel look around the environment at the eye height of the avatar providing an immersive experience. Is key we believe in providing effective pain relive for participants.

ADL exercises were developed for the participants to partake during the clinical study sessions. These included:

- An exercise inspired by the standardised blocks and box test. To which participants enjoyed building structures and towers.
- A cleaning exercise allowing the participant via grasping an eraser to clean a painting filled with dust.
- A shopping exercise in which the participant is placed in front of a conveyer belt in a virtual grocery store with moving items.The participant reaches to grasp objects and placing them in a basket. A list is displayed showing correct items to pick up and place in said basket.

2.2 Clinical Study

2.2.1 Methods

This paper presents the results obtained with five brachial plexus case studies recruited to the AMPSIM clinical study from the RNOH Stanmore cohort (Mean age - 39.2 years SD - 14.4 and Mean time since amputation - 8.3 years, SD 12.5) who have fully completed the robotic intervention and follow up assessments. An overview of the participants can be found in Figure 1. The two groups correspond to those who **did not** experience force feedback (control) and those who **did** experience force feedback. Participants were randomly assigned to each group. The study was approved by the NHS ethical committee and is on the NIHR portfolio. (IRAS Project ID: 179870 ; REC Reference: 15/WM/0147)

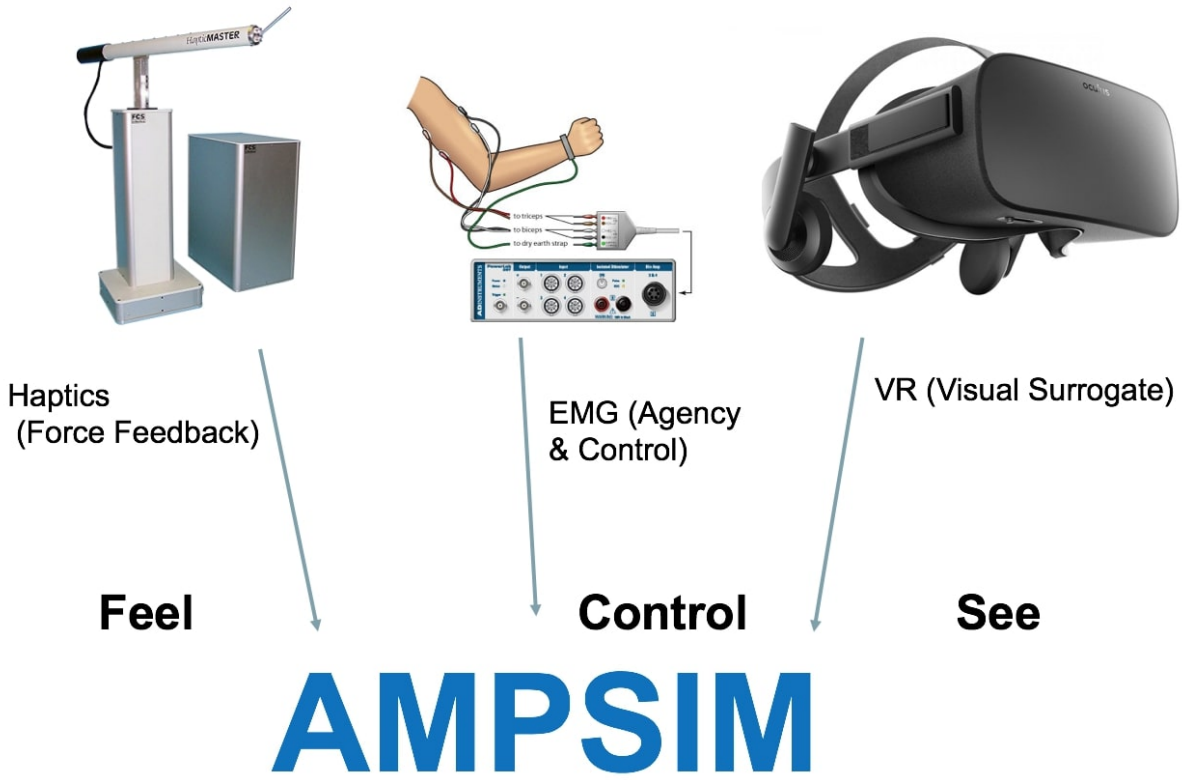

Figure 2. The three main and unique elements that make up the AMPSIM system. Feel, Control and See.

2.2.2 Participants

P1 is a male transhumeral amputee, 58- year-old at the time of the study, who was assigned to the control group. The amputation was a result of a traffic accident losing his right arm and leg 30+ years ago. P1 had his amputation immediately after this accident and experienced Phantom Limb Pain straight after the operation, being prescribed medication (Pregabalin and Gabapentin) ever since. During the initial pre pain questionnaire P1 stated that he found the medication (out of a scale from 1-5, 1 being very ineffective to 5 being very effective) to be 1 out of 5. P1 has been a body powered prosthesis user since the amputation (dominant hand was his left side). P1 had little or no control of their Phantom hand along with poor Phantom hand representation.

P2 is a male transhumeral amputee, 26-year-old at the time of the study, who was assigned to the experimental group. The amputation was caused by a traffic accident losing his right arm (also his dominant side) over 2 years ago. An above the elbow amputee who's onset of Phantom Limb Pain began a year after amputation. P2 did not take any medication for the pain at the time of the study, but had been prescribed medication immediately post amputation to which the participant found the effectiveness to be 3 out of 5. P2 is a cosmetic prosthesis since the amputation, with some control of their Phantom hand and fairly good Phantom hand representation.

P3 is a female transhumeral amputee, 36-year-old at the time of the study, who was assigned to the control group. The amputation was caused by a motorbike accident just over a year ago. P3's Phantom Limb Pain started as soon as she came around after an induced coma, a month after the accident. P3 has been on pain medication immediately since the amputation, required various operations post amputation

due to the severity of the accident. Due to the level of amputation P3 did not use a prosthesis eventhough having one provided to take part in the study. P3 similar control and representation of their Phantom hand to P2.

P4 is a right handed male, transradial amputee, age 26 at the time of the study, who was assigned to the experimental group. P4's amputation was as a result of a motorbike accident six years ago. Pain started since the accident and brachial plexus injury. He has been on a combination of medications for the pain (Gabapentin and Amitriptyline) since the accident. During the initial pre pain questionnaire P4 stated that he found the medication to be 3 out of 5 effective. P4 has been a cosmetic non-functional prosthesis user since the amputation, successfully incorporating the prosthesis into his work. P4 had some control of their Phantom hand and achieved fairly good representation of their Phantom hand.

P5 is a right handed female, 50-year-old transradial amputee at the time of the study, who was assigned to the control group. 10 years prior to the study the participant sustained a brachial plexus injury due to a motorbike accident subsequently chose to have an amputation electively 2 years after the accident. P5 was on Pregabalin for the pain since the accident. During the initial pre pain questionnaire P5 stated that he found the medication to be 2.5 out of 5 effective. Although P5 was provided a cosmetic prosthesis, she did not wear it day to day. P5 had extremely limited control of their thumb in her Phantom hand and poor Phantom hand representation, possibly due to the nature of the accident.

Three participants were on medication for pain related to either their brachial plexus injury or Phantom Limb Pain, with one participant not taking medication for pain. Using a standard pain assessment sheet during the preparation session a linker scale was used from 1-5 (Very ineffective to Very effective) to measure the participant's effectiveness of the medication on treating their pain. The average score was 2.5 (STD 0.9) reflecting the current state of research on the effectiveness of pharmacological intervention for this type of pain. In addition, three participants in this cohort used a prosthesis with two not using a prosthesis. An overview of the participants can be seen in Table 1.

2.2.3 Measures

A number of primary and secondary outcome measures were used to assess changes in reported pain, embodiment, and psychophysiological responses to quantify therapy effectiveness. In this paper we report on the perceived pain and embodiment measures using the following:

- Initial Pain Questionnaire (Bendinger and Plunkett, 2016)
- Per session McGill Pain (Short) Questionnaire (Bendinger and Plunkett, 2016)
- Botvinick's Embodiment Questionnaire (Botvinick and Cohen, 1998)
- Proprioceptive Drift Estimation (Wold et al., 2014)
- Pain Diary

We do acknowledge that the effect of novelty might have an impact on the results. However all steps to reduce this effect were taken.

2.3 Study Timeline

Figure 3 highlights the study timeline that all participants followed. An initial meeting was taken before any therapy sessions which the study was further explained and consent was taken. This was followed later by a preparation session if consent was given in which sensors were set up and EMG pattern recognition

was carried out for each participant. An initial pain questionnaire was also taken along with allocation of a pain diary during the preparation session.

The therapy sessions took part in the subsequent three weeks. Which resulted in nine sessions (1 hour each consisting of donning and doffing the equipment, exercises with the robot and questionnaires) spread evenly, 3 sessions per week. The proprioceptive drift estimation was taken before and after each session. With the short McGill and Embodiment questionnaires conducted at the end of session. Any sensor/kinematic/kinetic data is automatically saved during every session.

After the last therapy session a post intervention period consisting of three weeks takes places without any perscribed therapy sessions.

Two follow up sessions six and twelve weeks since the clinical study starts, are then carried out, where a short interview is conducted along with the short McGill and proprioceptive drift measurements.

Figure 3. Flowchart showing the study time line.

3 RESULTS

3.1 Case Study I - P1

Figure 4 shows the McGill score and embodiment level for P1. Initially the data does suggest a correlation with regards to a decrease in perceived levels of pain reported and an increase in reported embodiment during the majority of sessions. The pain does seem to go up from session 6 to the last of the therapy sessions by one point, but still below the base level pain. A jump between the last therapy session and the two follow up sessions does appear, however the participant noted in their interviews that other factors could have potentially contributed to this spike in perceived pain levels. P1 noted in their pain diary that post session 9 for a week and a half, so half way until the first follow up session that little or no pain was experienced. P1 stated that it took a few sessions for him to truly believe that it was himself controlling the virtual hand fully using his residual muscles. This delay in believing and subsequence surge in sense of agency could be indicative of why there is a jump in the level of embodiment around the 4th session mark. P1's pain diary stated that the levels of pain during the intervention period during the time not on the robot was on average 1.9/5 (Standard deviation 0.98) whilst post intervention the average pain recorded was 2.9/5 (Standard deviation 1.27).

P1 experienced a 10% decrease in pain during the nine sessions and 20% increase from the final session to the second follow up session.

3.2 Case Study II - P2

P2, another experienced prosthesis user was placed in the experimental group (VR + Haptics). Experiencing the best levels of pain reduction out of the 5 participants reported in this paper. Figure

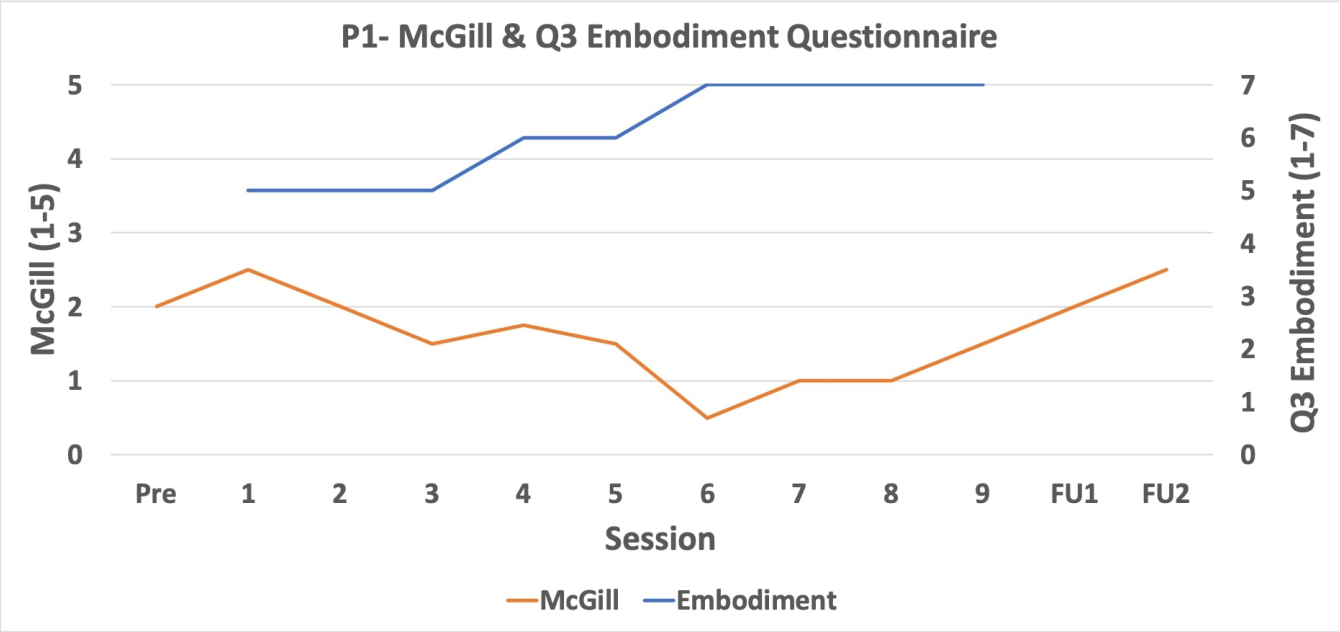

Figure 4. Mcgill score and embodiment question graph for participant P1.

5 shows P2's pain and embodiment levels during the whole study, showing that by the 3rd session P2 perceived no pain either during the sessions. Although the pain levels remained low P2 did report 12 short (seconds - 10 mins) of pain episodes (average of 2/5 Standard deviation 1.42) self reported in the pain diary after the therapy sessions.

Despite these 12 short pain episodes, P2 described how he utilised techniques he had learnt during the therapy session such as distraction or imagining performing the one of the exercises as tools to help better deal with the pain episodes.

P2 took part in the clinical study around a year post amputation and thus as a recent amputee might account for the effectiveness seen in his results. There seems to be a strong link with P2 in terms of strong embodiment and sharp decrease in perceived pain.

P2 experienced a 80% decrease in pain during the nine sessions and no change from the final session to the second follow up session.

3.3 Case Study III - P3

Pain and Embodiment levels for P3 are shown in Figure 6 and suggests that the participant's pain levels fluctuated during the sessions. The level of embodiment appears to be low unlike the previous participants so far. This could be attributed to the participant being a non prosthesis user and also not engaging with the prosthesis in-between sessions. Partly due to her limited range of motion made worse by post amputation surgery which severely impacted movement, leading to a view of not wanting to use a prosthesis with such a loose fit of the quickly made prosthesis for the study. The spikes in pain levels could also be attributed to the start of a new week of intervention.

P3 experienced a 10% increase in pain during the nine sessions and a 10% decrease from the final session to the second follow up session.

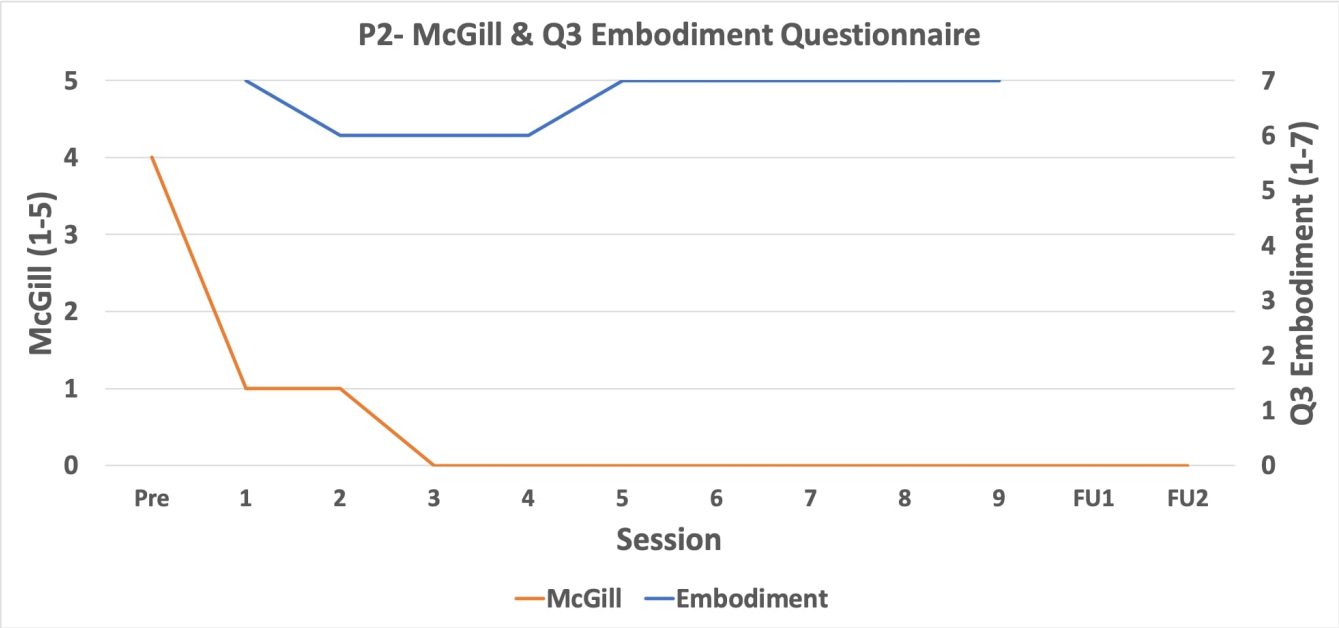

Figure 5. Mcgill score and embodiment question graph for participant P2.

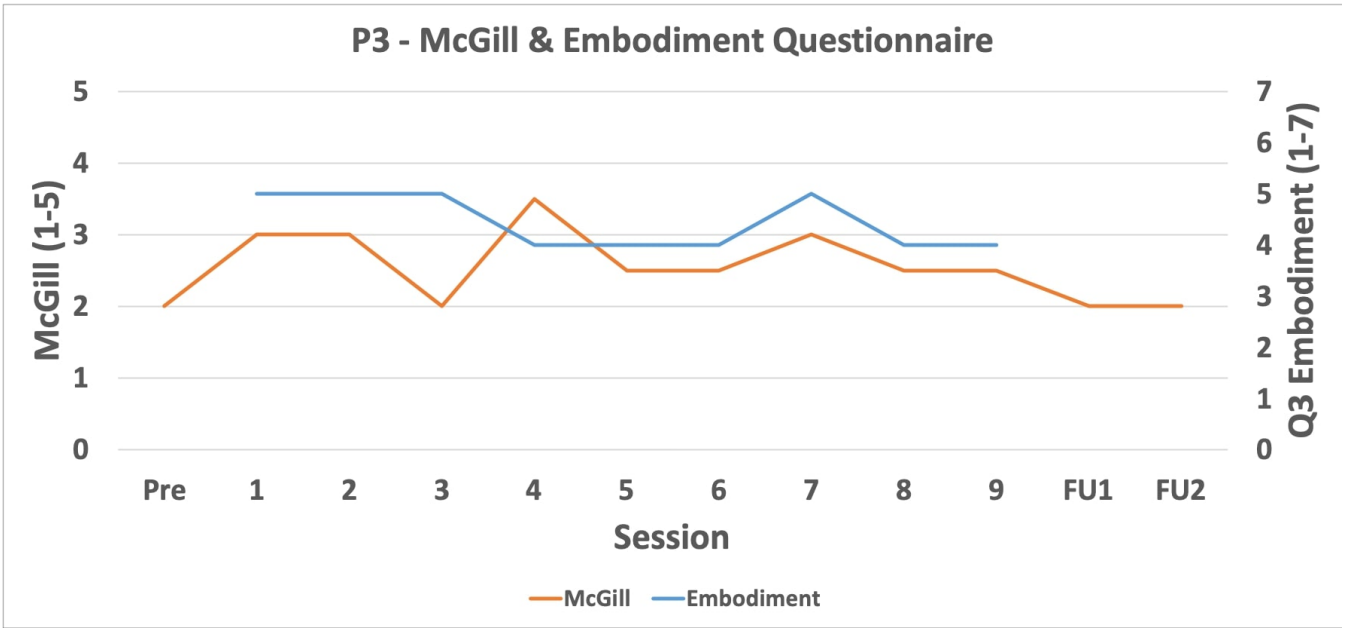

Figure 6. Mcgill score and embodiment question graph for participant P3.

3.4 Case Study IV - P4

P4 as shown in the Pain and Embodiment levels (Figure 7) showed strong embodiment with associated pain decrease. This could perhaps be explained by the participant's experience of prosthesis use in day to day life and incorporating the prosthesis in his work too. The drop in levels of embodiment shown in session 4 could explain the knock on effect on pain levels shown in sessions 5 and 6 due to the fact that the previous and subsequent sessions show stable levels of pain recorded.

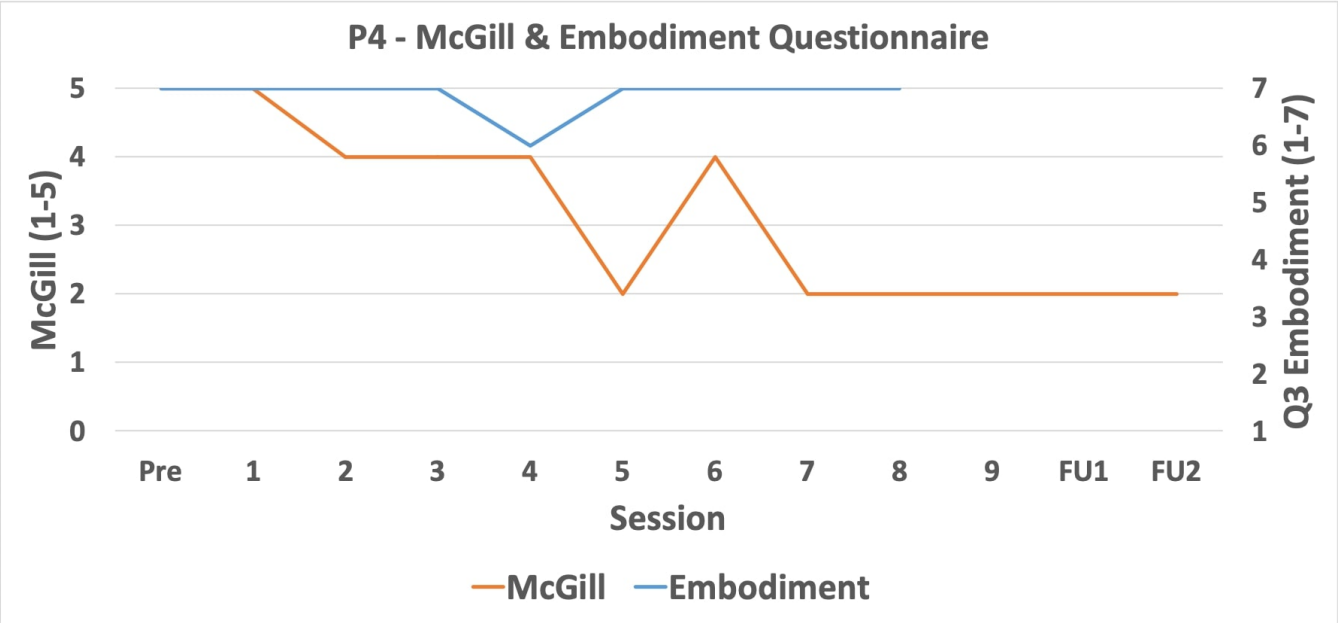

Figure 7. Mcgill score and embodiment question graph for participant P4.

P4 experienced a 60% decrease in pain during the nine sessions and an 20% increase from the final session to the second follow up session. Pain levels reached 50% decrease at session 5 with the participant experiencing an improvement in both function and representation of the Phantom hand.

3.5 Case Study V - P5

Pain and Embodiment levels for P5 are shown in Figure 8 similar to P3 experiencing poor levels of embodiment and pain levels that fluctuate. However a decrease to 50% of baseline pain scores occurs in sessions 2 then 7. Despite these fluctuating levels there does seem to be some sort of correlation between rising levels of embodiment and lowering levels of pain reported.

P5 experienced a 40% decrease in pain during the nine sessions and an 20% increase from the final session to the second follow up session.

4 DISCUSION

As a whole, the group did on average experience pain reduction as shown in Figure 9. There does seem to be jumps in pain levels from the session at the end of the first weeks to the second week (sessions 3-4) which is understandable due to the gap between sessions. Regardless of the intervention group (control or experimental) the general decrease is followed by relatively small increases in pain levels during the two follow up sessions 3 and 12 weeks post session 9.

All of those participants, attributed with high baseline pain (P2, P4 and P5), achieved a 50% (scaled) decrease at some point or cumulatively pain reduction during the study. As show in Figure 10. Suggesting that those with higher baseline pain benefit greater than those with mid or lower levels of baseline pain. The time it took for the participants in the high pain group to reach a 50% decrease in pain was 2.7 sessions which amounts to less than 3 hours of intervention (STD 2.1 sessions).

Breaking the participants into the intervention groups also shows the effectiveness of the experimental group which had the addition of haptics as shown in Figure 11. With steeper decreases of pain levels found

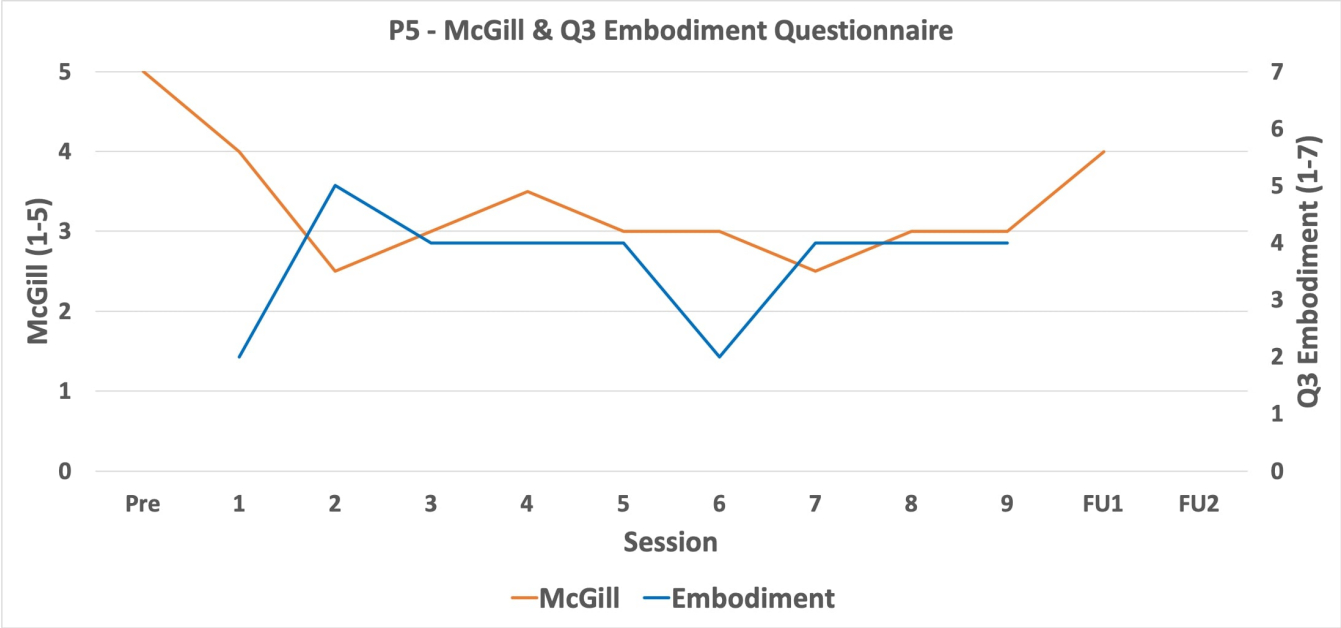

Figure 8. Mcgill score and embodiment question graph for participant P5.

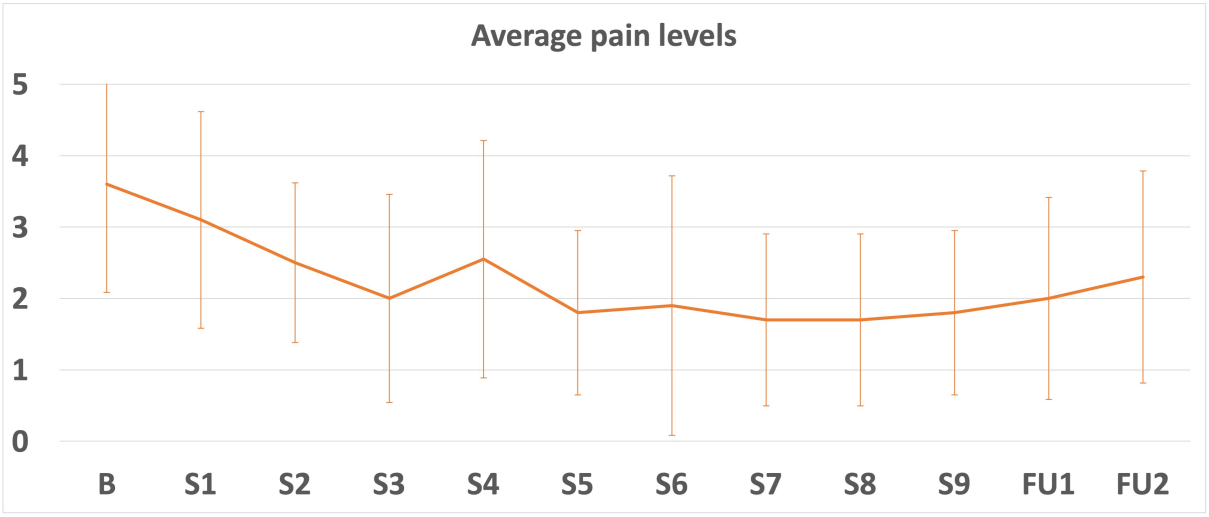

Figure 9. Average pain levels for the five participants. On a 1-10 scale.

within the experimental group in comparassion to the control group. Despite a sharper increase in pain levels from follow up 1 session to the final follow up session in the experimental group the levels hold quite well.

5 FUTURE WORK

The initial results suggest promising results with the use of the virtual reality and robotic system. It does seem that those who experience haptics do report a sharper decrease in pain.

Combining our paradigm in the clinic with a ”take home” system consisting of a phone based application, a powerful phone and headset such as the Samsung Gear VR or similar could potentially yield further sustained decreased levels of pain and greater range of motion over a longitudinal study.

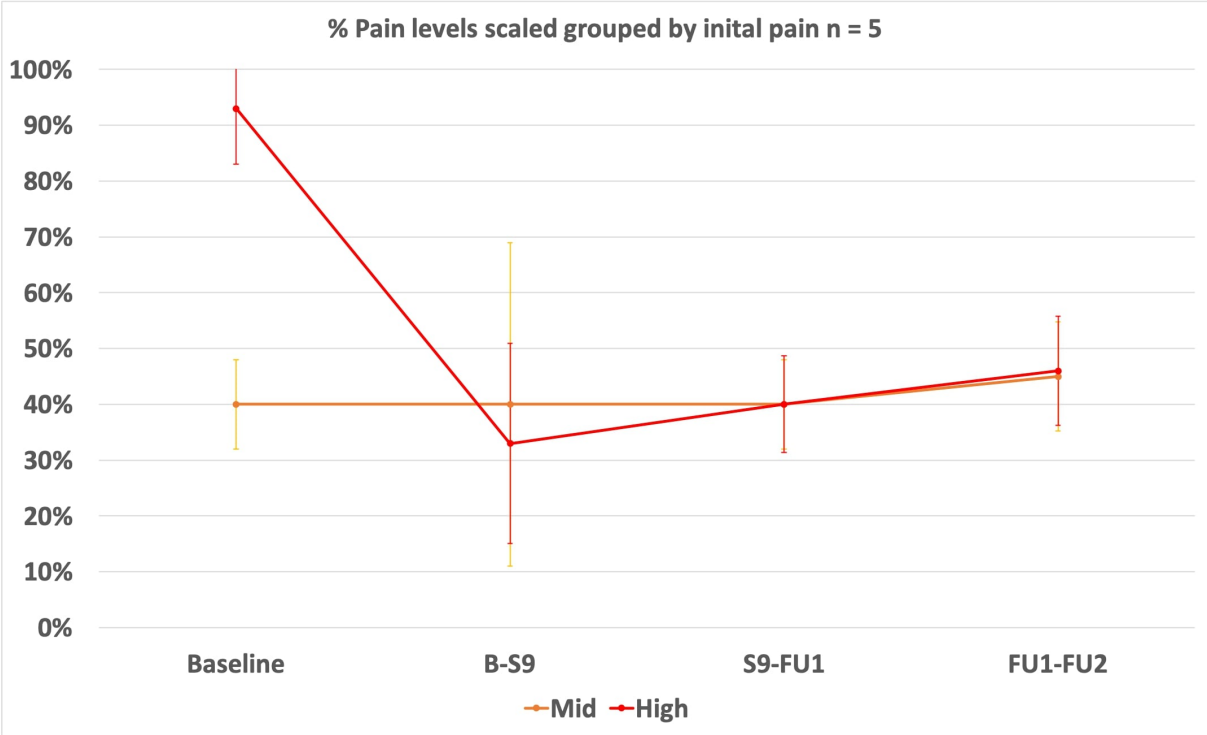

Figure 10. Scaled percent changes by initial pain levels

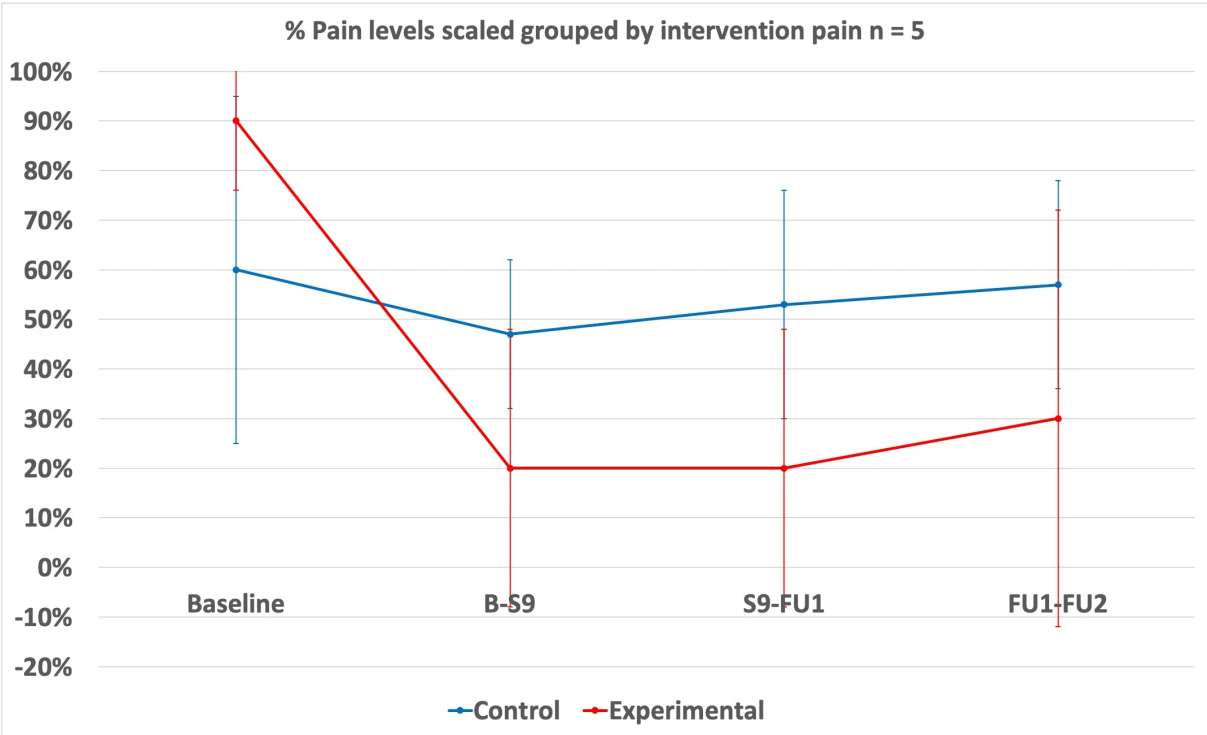

Figure 11. Scaled percent changes by initial pain levels

Complying to a UE4 phone application is straight forward and the use of an external controller could be set to track the amputated arm.

EMG sensors connected to a bluetooth enabled arduino such as the Bionic Clicker by Magee et al (Magee et al., 2017) could be used as a simple EMG interface in lieu of an amplifier used in the main system.

6 CONCLUSIONS

This paper has detailed an immersive virtual reality and haptic robotic system which allows participants who have suffered traumatic brachial plexus injuries, resulting severe lack of range of motion and pain to take part in non invasive therapy to help alleviate these outcomes post injury. To ”hide” and artificially correct range of motion issues via the immersive system enables such patients to access much needed help when traditional interventions have not yielded sufficient results. Overall the participants found benefits not just in pain levels but in other areas such as sleep, movement and posture. The non invasive element of this paradigm suggests that it could be used as an intervention at an earlier stage of a patient's recovery which may provide better therapy outcomes.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

The Author Contributions section is mandatory for all articles, including articles by sole authors. If an appropriate statement is not provided on submission, a standard one will be inserted during the production process. The Author Contributions statement must describe the contributions of individual authors referred to by their initials and, in doing so, all authors agree to be accountable for the content of the work. Please see here for full authorship criteria.

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PartID	Group	Baseline Pain	Level	Prosthesis Used	On Medication
P1	Control	2	TH	Y	Y
P2	Experimental	4	TH	Y	N
P3	Control	2	TH	N	Y
P4	Experimental	5	TR	Y	Y
P5	Control	5	TR	N	Y

Table 1. Participant table. In which the baseline pain is out of 5. TR = Transradial and TH = Transhumeral

Appendix B

Protocols

RESEARCH PROTOCOL

Version 3.0

12.09.2016

Title: A pilot study to compare Virtual Reality (VR) versus VR plus haptic feedback as a possible technique to decrease upper limb phantom pain responses in amputees

Nature of project: A study on original research to provide a preliminary evaluation of virtual reality haptic therapies. This research forms part of a PhD programme, through the Dstl National PhD scheme.

Project Management Members

Chief Investigator:
Dr Rui Loureiro
Visiting Associate Professor / ASPIRE Senior Lecturer
School of Science and Technology / UCL Institute of Orthopaedics and Musculoskeletal Sciences
Middlesex University / University College London
The Burroughs, Hendon, London, NW4 4BT / Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, HA7 4LP
Telephone: 0208 385 3049
E-mail: R.Loureiro@ucl.ac.uk

Other Investigators:
Prof Richard Comley, Director of Research, Middlesex University.
Mr Peter Snow, PhD student undertaking the work at Middlesex University.
Ms Annalise Whittaker, Dstl Technical Partner.

Clinical Investigators:
Dr Imad Sedki, Consultant in Rehabilitation Medicine, Prosthetic Rehabilitation Unit, Royal National Orthopaedic Hospital, Stanmore.
Dr Marco Sinisi, Consultant Neurosurgeon, Peripheral Nerve Injury Unit, Royal National Orthopaedic Hospital, Stanmore.
Miss Caroline Hing, Trauma & Orthopaedic Surgeon, St George's Healthcare NHS Trust.
Kate Lancaster, Senior Physiotherapist, Douglas Bader Rehabilitation Centre, Queen Mary's Hospital, Roehampton.
Note: The clinical investigators will provide clinical advice and assistance with recruitment of participants to the study.

Table of Contents

1. INTRODUCTION

Blast injuries in modern warfare result in fewer fatalities, largely due to improvements in body armour, but survivors have multiple injuries including lung damage, fragment injuries, traumatic brain injury and traumatic amputation of limbs (Taber et al, 2006). The decision as to whether to attempt limb salvage or an amputation is difficult but in either case there are subsequent problems with rehabilitation including phantom pain and limb non-use (Russell et al, 1991). Phantom limb phenomenon affects a large percentage of amputees (50-80%) and results in feeling body parts that are no longer there (Giummarra and Moseley, 2011). Amputated limbs can ache, itch, burn, feel dry or wet, tense, locked or stuck, or even feel they are moving (Hunter et al, 2003; Giummarra and Moseley, 2011).

The effects of Phantom Limb Pain (PLP) can worsen due to anxiety/stress and other factors (Giummarra and Moseley, 2011). Not only does this affect the individual's mental wellbeing (coping with the psychological trauma associated with the limb loss) but also their physical state (imposed by the chronic pain effects) and the rehabilitation outcome (Arena et al, 1990). Regional rehabilitation units, Defence Medical Rehabilitation Centres and NHS rehabilitation centres are posed with diverse challenges as the individual experiences emotional discomfort in addition to psychological trauma, reduced mobility and Phantom Limb Pain (Horgan & MacLachlan 2004).

1.1 BACKGROUND

There is a substantial body of work on Phantom Limb Pain using visual surrogates. A recent review of the field is given by (Giummarra and Moseley, 2011). It is clear from the work of Ramachandran & Blakeslee (1998), Cole (2004) and others (Murray et al, 2006) that there are benefits to providing a visual surrogate for the missing limb which likely allows stimulation of unused areas of the motor cortex. Ramachandran's mirror box therapy, where the subject sees a reflection of their intact limb situated where their amputated limb should be, is further supported by the work of Lotze and colleagues who show evidence of cortical reorganisation (Lotze et al, 2001). Ramachandran and others report that when a person is able to perceive and appear to be connected to their missing limb they report a reduction in phantom limb pain typically measured using self-reporting questionnaires such as the McGill pain questionnaire (Katz, 1992; Hunter et al, 2003; Murray et al, 2006; Giummarra et al, 2010). Cole and later Murray and colleagues investigated more advanced methods of providing this treatment using virtual realities (Murray et al, 2006).

There is evidence to suggest that phantom limb pain is connected with the idea of an internal feed-forward model (an internal process that simulates the response of the motor system in order to estimate the outcome of a motor command). This model uses both an internal copy of the outgoing motor commands (efferent) along with afferent sensory signals (information sent from the peripheral nervous system back to the brain) to estimate the current and the immediate future state of the limb (Kawato 1999; Giummarra and Moseley, 2011). In this theoretical model the suggestion has been made that the maladaptive reorganization, which takes place in the sensorimotor cortices and descending motor pathways, disrupts the integrity of sensory feedback in amputees leading to a mismatch with the comparator movement that causes phantom limb pain. The absence of feedback from the missing limb to the intact motor system produces the mismatch that amplifies the pain. Taking this into account, one can argue that Ramachandran's mirror box therapy works because the

brain has an afferent copy, that it is moving the limb, followed by visual feedback that the limb is moving. This process is consistent with motor planning, and that actually reduces the pain. So, it is about the planned movement and the sensory feedback consistent with the planned movement. The suggestion then is that when one gets feedback that is consistent, i.e. one sees the limb moving while the brain is telling the phantom limb to move, it re-calibrates the internal model and that reduces the pain. However as reported in the literature this principle does not seem to work every time. A recent publication (Giummarra and Moseley, 2011) reviewing various phantom limb pain treatments highlight that each mechanism can be triggered by physical sensations, can have psychological/emotional origins (in the case of an amputation) and could also arise from climate-induced triggers, like temperature or changes in weather. These triggers where investigated by Guinmarra and colleagues (Giummarra et al, 2010) who have shown the need for optimising stump and neuoma mechanisms to manage spontaneously triggered phantom phenomena.

Embodiment has been described as the sense of one's own body (Longo et al, 2008) which when examining the effects of a virtual surrogate limb on the amputee population is an important area to study. Both visual and multisensory cues can lead to embodiment (Zopf et al, 2011; Arzy, 2006). Some amputees who use either standard functional or myoelectric prostheses[1] experience vivid Phantom Limb Phenomena (Hunter et al, 2003) but reduced Phantom Pain (Kooijman et al, 2000; Lotze et al, 1999). Such results can be explained by the fact that once an amputee engages with the prosthetic limb their proprioception extends to embody the prosthesis (Giummarra et al, 2010; Preester and Tsakiris, 2009).

Several strategies have been devised to enhance limb embodiment (magnifying the limb seems to increase pain, whereas making the limb look smaller seems to reduce pain) with virtual realities with varying degrees of success (Ehrsson et al, 2008; Slater et al, 2009; Schmalzl and Ehrsson, 2011). Most studies however, have shown more vivid embodiment within amputees whose phantom limb is extended and equates to a sensory map on the amputated stump (Ehrsson et al, 2008). Paradigms such as the rubber hand illusion have been shown to provide the amputee with a greater sense of embodiment if the amputation is recent (Giummarra et al, 2010) with further research showing that tactile feedback enhances the embodiment of a prosthetic limb (Marasco et al, 2011). It is also suggested that proprioceptive feedback enhances targeted motion within upper limb prosthesis control (Blank et al, 2010).

1.2 RATIONALE

Studies on Phantom Limb Pain thus far have been mostly on short-term exposure to a particular intervention (Cole 2004; Murray et al, 2006) and the focus on embodiment with virtual realities has not considered proprioceptive modulation using force feedback through a haptic interface that can move in three-dimensional space in conjunction with a visual surrogate (Giummarra and Moseley, 2011). Most of the work in the field (Giummarra and Moseley, 2011) has been driven by the assumption that cortical reorganisation is occurring; possibly including so called mirror neurons that fire in advance of a movement or when a movement is perceived (even when done by another person). The concept is to encourage cortical reorganisation so as to reduce the perception of pain and to regain control of the residual limb. This cortical reorganisation is similar in essence to our

[1] Prosthetic devices that use signals from voluntarily contracted muscles within a person's residual limb on the surface of the skin to control the movements of the prosthesis.

work in stroke rehabilitation (Amirabdollahian et al, 2007; Loureiro et al, 2009; Loureiro et al, 2013) where motor areas of the brain are retrained to regain control of the hemiplegic limb. In stroke the concept of learned non-use is common and the use of robotic and haptic interfaces appears to offer promise in retraining limbs. In a recent randomised control trial on robot therapy to treat stroke (NCT00372411, 2010), the U.S. Veteran Affairs department stopped the non-intervention phase since it had sufficient evidence of the effectiveness of the robot based treatment. What is lacking at present is information about the nature, intensity and effectiveness of behavioural treatments that attempt to use these ideas to treat Phantom Limb Pain and salvaged or residual limb non-use.

Based on the above, we hypothesise that by providing force feedback through a haptic interface that can move in three-dimensional space in conjunction with a visual surrogate for the missing limb while interacting with a virtual object in an immersive virtual reality environment, will enhance embodiment and result in a higher reduction of perceived pain than with a visual surrogate without force feedback.

To test the hypothesis we will evaluate the effect of immersive virtual haptic therapies on perceived pain using a sensorimotor training system that provides direct physical contact with a haptic device, mapping of the information from the device to the virtual representation of the physical limb and an application that maintains challenge and interest to the individual.

2. STUDY OBJECTIVES

The proposed study will establish a more solid scientific framework for advancing the knowledge of haptic interaction in the treatment of Phantom Limb Pain and its outcome will be used to inform a future phase II trial to quantify the new approach in terms of cost benefit and therapeutic practice. The knowledge gained and the prototype developed will have applications in general robotics and rehabilitation. In the long term it could offer the potential to increase the possibility of retaining trained military personnel following trauma by providing the basic tools leading to the development of the next generation of sensorimotor control strategies, aiding in the design of more efficient prosthesis, as well as the integration with portable and cheaper therapy systems, thus opening up possibilities for training in remote and unsupervised environments.

The proposed innovation is intended for future use in military regional rehabilitation facilities, but clearly has more general application in NHS regional rehabilitation centres for the treatment of non-use of salvaged and amputated limbs and is likely to be effective for research on the treatment of Phantom Limb Pain. The research will benefit service men and women, and clinical providers of their rehabilitation treatments. The proposed research innovation may also have potential to reduce costs of rehabilitation but a more detailed research is needed to address this question.

2.1 PRIMARY OBJECTIVE/S

To measure the effectiveness of an immersive Haptic system that combines a visual surrogate for the missing limb with haptic feedback (VR + Haptics) on reducing phantom limb pain, as compared with the same therapy without the haptic feedback (VR only).

2.2 SECONDARY OBJECTIVE/S

To assess how the short and longer-term effects of the therapy affect embodiment and perceived phantom limb pain.

2.3 STUDY OUTCOME MEASURES

Physiological sensor information is used to quantify psychophysiological responses to the audio-visual and haptic cues provided by the AMPSIM system (see Figure 1 and Figure 2). Perception of the environment (and from the haptic cues) will invoke proprioceptive and exteroceptive user responses that will result in motor actions and a subsequent response (e.g. movement of the limb, feeling the weight of an object). Possible motor control actions are picked up by a range of different biomechanical sensors (present in the haptic device), by the HMD (head tracking) and kinematic tracking of the residual (and intact) limb. Below is a summary and justification for the different outcome measures used in the study:

Primary outcome measure:

- McGill pain (short) questionnaire: used to measure perceived levels of pain experienced by the participant taken at the beginning of the study, at the end of each therapy session and at a follow up session.

Secondary outcome measures:

- Botvinick's embodiment questionnaire: used to measure perceived levels of embodiment (limb ownership) that the participant may experience, which is taken at the end of each session.
- Proprioceptive drift estimation: used to measure the perceived level of embodiment before and after the intervention session. This measure consists of the distance the participant perceives their limb has moved. Two measurements (participant points to where they think the center of their hand is) are taken one before and another after the exposed immersion (before/after each session). The difference is produced and used as the measure of proprioceptive drift.
- Pain diary: participants will be asked to keep a pain diary for the length of the study until final follow up.
- Galvanic skin response (GSR) and respiration: used to measure the stress and workload during execution of the tasks. An increase magnitude in these measures has been shown to indicate higher level of stress and workload. GSR will be taken via disposable self-adhesive gel electrodes placed on surface of the skin. Respiration will be taken by placing a sensor on the nostrils.
- Circle on the table: participants will be asked to place their intact hand on a specific area on the virtual/real table while exercising and to remove the hand from the table when pain is perceived during each session. This will be used as a marker of the onset of perceived pain to aid correlation with the physiological measures.
- Electromyography (EMG) pickups: EMG pattern recognition via surface electrodes will be used purely to capture muscle activity within the residual limb to detect grip formation and release during the games. Disposable EMG self-adhesive gel electrodes are placed on surface of the skin on the residual limb.
- Kinematic data: both residual and intact limb movement profiles will be captured from the 3 degrees of freedom haptic device and through a tracking system. Like the GSR and

respiration levels, the kinematic data will be used in conjunction with the circle on the table to examine any effects relating to movement quality (e.g. smoothness) that participants might experience as a result of perceived pain.

3. Study Design

The haptic system (AMPSIM) will be installed at the Aspire Centre for Rehabilitation Engineering and Assistive Technologies (directed by the chief investigator) located at the Royal National Orthopaedic Hospital. Although this will be the preferred location for the study, should the need arise, we might consider moving the AMPSIM system closer to any of the other rehabilitation centres identified below should this prove more practical for certain participants.

3.1 APPARATUS

Participants in the study will be performing motor tasks using our immersive haptic sensorimotor training system (see Figure 1 and Figure 2) that provides:

1. direct physical contact to the haptic device,
2. mapping of the information from the device to the virtual representation of the physical limb,
3. and an application that maintains challenge and interest to the individual.

Based on these elements, the haptic system acquires Electromyography (EMG) commands, residual limb kinematics and displays the combined residual limb movements in a virtual reality environment that includes force-based interactions with virtual objects. Visualisation is provided via a Head Mounted Display (HMD) so as to facilitate first-person view of the virtual environment and embodiment of the residual limb with virtual representation.

The HapticMASTER is a commercially available haptic device (Van der Linde et al, 2002) capable of generating forces in 3 dimensions. In conjunction with the custom-made 3 degrees of freedom gimbal, it facilitates movements in 6 degrees of freedom. Forces can be generated to simulate the physical properties of virtual objects, such as a geometry, texture and weight, collisions with objects or to assist with arm movements (Loureiro et al, 2003; 2011).

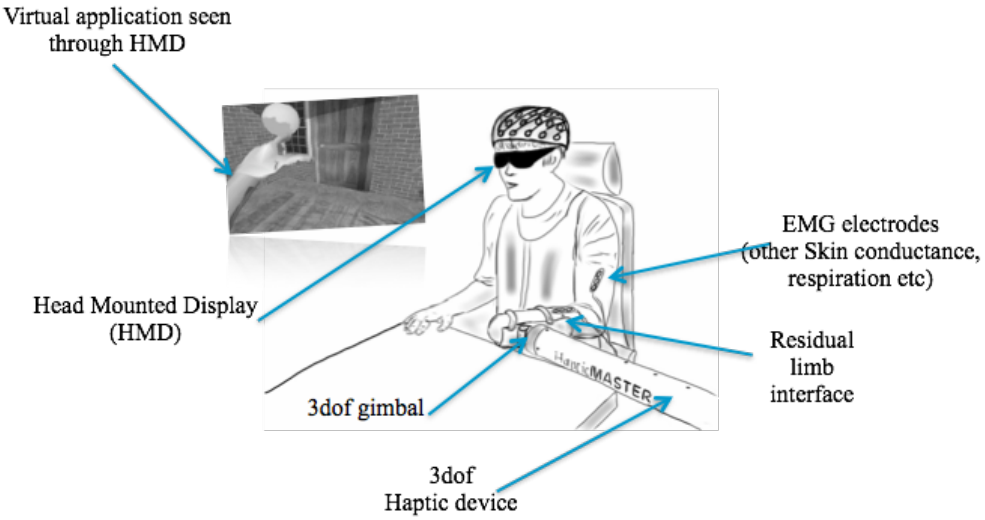

Figure 1: Conceptual illustration of the haptic immersive training system (AMPSIM).

Figure 2: Able-bodied individual using the AMPSIM training system while wearing a head mounted display (HMD). Top left image is the virtual application seen through the HMD.

3.2 TASKS

Participants in the study will be performing (virtual) tasks designed to facilitate unilateral and bilateral movements (Figure 3). The tasks are designed to promote motor learning and also where possible, double up as assessment. One example is an adaptation of the original 'box and blocks test' (BBT) a quick, simple test used frequently to measure unilateral gross manual dexterity with a wide range of populations such as stroke. The original BBT exercise requires moving small blocks from one compartment of a box to another separated by a divider (Mathiowetz et al, 1985). Other tasks include manipulation of objects in scenarios of the daily living such as organising a shopping basket on a supermarket, setting the table for dinner, picking fruit to make juice, and cleaning a picture frame to reveal an image.

Figure 3: Virtual ADL tasks available in AMPSIM.

We use computer aided visual tracking to capture position and orientation information from the intact limb and kinematic tracking using the haptic device with the residual limb interface. To detect grip formation and release in the residual limb, we are using simple Electromyography (EMG) pattern recognition methods based on a minimum of four EMG electrode pickups as described by (Naik et al, 2006; Naik et al, 2008) and other classification techniques (Scheme & Englehart 2011; Kim et al, 2008; Micera et al, 2011).

3.3 SPECIFIC METHODS

Participants (minimum of 20, 10 in each group: please see section 4.6.2 for sample size justification) will be assigned to one of two treatment groups and interact with the system through virtual representation of the limbs:

1. VR + Haptics group: visual surrogate for the missing limb with haptic feedback (VR + Haptics).
2. VR group: visual surrogate for the missing limb without the haptic feedback (VR only).

The setup for both groups is the same (i.e. both groups will be connected to the 3 degrees of freedom haptic device via a residual limb interface) but the VR group will interact with the tasks without haptic feedback (i.e. the 3 degrees of freedom haptic device is used only to measure the residual limb kinematics).

Table I summarises the study time line. At least 24 hours will be allowed between briefings and provision of written informed consent for participation in the study. In addition to the baseline measurements and final follow up, a number of outcome measures, as summarised in section 2.3, will be employed (by the experimenter) at the beginning and end of each therapy session. To account for variations on effects in between sessions and final follow up, participants will be asked to keep a pain diary for the length of the study until final follow up.

Table I: Study time line

Session	**Activity**	**Duration**
Initial meeting	• Explain the purpose of the study and answer any questions • Provide written informed consent for participation in the study	30-60 min
Preparation session	• Determine the set up of the different sensors • Establish a simple EMG pattern recognition from the participant's residual limb • Moulding a residual limb interface cuff to the haptic device for comfort and function. • Take initial Pain questionnaire • Pain diary provided for the duration of the study	60-90 min
Intervention session (3/week, 1 hour each) Weeks 1-3	• Set up sensors • Measure proprioceptive drift • Perform tasks with AMPSIM (take up to 10 min break if necessary) • Measure proprioceptive drift • Take off the sensors • Complete the embodiment and the McGill Pain questionnaire	Initial 10 min 60 min Last 10 min
Post intervention Weeks 4-12	• Participants are asked to keep a Pain diary • No formal training received	NA
Follow up session Week 6	• Take Pain questionnaire • Conduct Interview • (determine if any reduction on perceived pain levels reported during first 3 weeks post intervention is retained)	30 min
Final follow up session Week 12	• Take final Pain questionnaire • Collect pain diary from participant • (determine if any reduction on perceived pain levels reported during the pilot study is retained at the end of 12 weeks)	30 min

The reported pain levels will be monitored with every session and reported to a qualified therapist (e.g. occupational therapist), which will decide on the need to follow it up with the participant. The therapist might decide to assess any psychological effects of taking part and determine what is the

probability of any physical discomfort to their affected limb be due to the experiment and the haptic feedback.

The decision for a training exposure of nine sessions over a three-week period is based on our experience with stroke clinical studies (Amirabdollahian et al, 2007; Loureiro et al, 2013) and further results reported in the literature showing that such exposure to robot therapy is often necessary to observe significant cortical reorganisation with the damaged brain and improved kinematic features (e.g. limb synergies and task oriented movements). A recent trial with similar therapy exposure has shown a 13.3% phantom limb pain decrease at the end of the study (Murray et al, 2006).

The Prosthetic Rehabilitation Unit and the Peripheral Nerve Injury Unit at the Royal National Orthopaedic Hospital (RNOH) will be the primary rehabilitation centres used for study. We also plan to recruit participants from St George's Healthcare NHS Trust and the Douglas Bader Rehabilitation Centre at Queen Mary's Hospital, London (Roehampton). The haptic system (AMPSIM) will be installed at the Aspire Centre for Rehabilitation Engineering and Assistive Technologies (directed by the chief investigator) located at the RNOH. Although this will be the preferred location for the study, should the need arise, we might consider moving the AMPSIM system closer to any of the other rehabilitation centres identified above should this prove more practical for certain participants. Although the system is not portable, i.e. does not allow for it to be easily moved on a regular basis between sites, it is possible to move it to other locations for longer usage periods.

4. PARTICIPANTS AND RECRUITMENT

4.1 Groups

As summarised in section 3.3 participants will be assigned to either the VR + Haptics group (visual surrogate for the missing limb with haptic feedback) or VR group (visual surrogate for the missing limb without the haptic feedback).

To ensure a good mixture of therapy abilities, we will consider both recent amputees and experienced prosthetics users provided they suffer from Phantom Limb Pain. Some studies reported in the literature have show

- differences in cortical reorganisation between subsets of amputees (Flor et al, 1998).
- long-term prosthesis use induces less vivid phantom limb sensations but the pain persisted.
- Non-traumatic amputees still experience phantom limb sensations and residual/stump pain, however this is less than traumatic amputees (Hunter et al, 2008; Limbless Statistics, 2013).
- Phantom Limb Pain regardless of the site of amputation leads to the same acute and chronic pain suffered by all patients (Murray et al, 2006).

Taking the above into consideration an effort will be made to balance the groups to include a similar number of participants with regards to the type, cause and length of time since amputation. Our system, in its current configuration, is most suited to support amputees with lesions below the elbow.

4.2 Inclusion criteria

- To ensure a good mixture of therapy abilities, we will consider both recent amputees and experienced prosthetics users provided they suffer from phantom limb pain.
- Participants with a stable biomechanical situation.
- Participants aged minimum 18 years old at onset amputation.
- All upper limb amputations.
- Above the elbow amputations might require participants to wear their prosthetic limb during the intervention.
- Amputations caused by dysvascularity (e.g. diabetes mellitus, non-diabetic arteriosclerosis, embolism, vasospatic conditions), which account for 52% of all new referrals for upper limb amputations in the UK.
- Amputations caused by trauma (e.g. mechanical, electrical, thermal, chemical) accounting for 10% of amputations.
- Amputations caused by infection (acute or chronic) accounting for 9% of amputations.
- Amputations caused by neoplasia (benign and malignant) accounting for 3% of amputations.

4.3 Exclusion criteria

- Participants outside the minimum age.
- Participants that do not adequately understand verbal explanations or written information given in English (or are not accompanied by an interpreter). In case of doubt on the participant's competency to consent, the investigator will seek advice from their GP/ rehabilitation consultant before proceeding.
- Participants without noticeable phantom pain.
- Participants whose residual limb and muscle activity cannot be used with the haptic device.
- Other medical reasons that participants are unsuitable to take part e.g. blind from diabetes, unstable psychiatric illness.

4.4 Withdrawal criteria

Any increase in pain, nausea or intolerance of the methodology.
The reported pain levels will be monitored with every session and reported to a qualified therapist (e.g. occupational therapist), which will decide on the need to follow it up with the participant. The therapist might decide to assess any psychological effects of taking part and determine what is the probability of any physical discomfort to their affected limb due to the experiment and the haptic feedback. The participant might be advised to not continue to participate in the study.

Should a major technical failure deem the system non-repairable or delays with such repairs take too long to complete the study within the project lifespan, participants will be informed and the study terminated. Although the risk associated with the reliability of the devices is low, as with any technology, it could have a high impact for the study to carry on as planned. The chief investigator has extensive experience in designing devices suited for application in clinical trial practice and has successfully run several clinical studies (inc. a multi-centre RCT). Durability tests will be performed with sensitive components during development, and a maintenance plan will be established in order to guarantee maximum availability of the devices.

4.5 Recruitment

Participants will be approached by their clinicians and therapists at the hospitals/centres identified above who will be familiarised with the inclusion/exclusion criteria and more generally in public spaces through advertising (e.g. posters), university and hospital webpages and social media such as twitter, facebook and forums)[2]. The participant information sheet (PIS) or a copy of the advert will be provided by the clinicians/therapists. Participants will then be directed to contact the research team using the information on the PIS or advert.

Potential participants identified as above would, following their expression of interest, be sent the PIS (if not supplied already) and be invited to attend an individual briefing session at their hospital/centre, where details of the project would be described and any questions answered. If, following this, participants want to sign up for the study; they will be invited to complete the consent form. At least 24 hours (up to two weeks) will be given for the participant to consider the information and consult others if necessary. Participants will incur no penalties if they decide not to take part in the study. The participant may leave at any time during the study without penalty.

4.6 Sample size

A minimum of 20 participants will be needed for the study, 10 in each group. Please see section 4.6.2 for sample size justification.

4.6.1 Sampling frame

The Prosthetic Rehabilitation Unit and the Peripheral Nerve Injury Unit at the Royal National Orthopaedic Hospital (RNOH) will be the primary rehabilitation centres used for study. Recruitment of participants from these units will be from patient databases under Dr Imad Sedki and Dr Marco Sinisi's case files. We also plan to recruit participants from St George's Healthcare NHS Trust (Ms Caroline Hing) and the Douglas Bader Rehabilitation Centre (Ms Kate Lancaster) at Queen Mary's Hospital, London (Roehampton); from the Harold Wood Disablement Services Centre, Harold Wood Hospital, London (Harold Hood); from the Southwark PCT Rehabilitation Centre, London (Bowley Close), and more generally from contacts at the Limbless Association.

Out of the 484 new upper limb amputee referrals per year in the UK, the combined London based centres account for 95 new referrals (Stanmore: 28; Roehampton: 37; Harold Hood: 18; Bowley Close: 12) (Limbless Statistics, 2013). We anticipate we will be able to recruit to the study between 20 - 30% of these new annual referrals with the remainder of participants being recruited from returning chronic patient databases under Dr Sedki, Dr Sinisi, Ms Caroline Hing and Ms Kate Lancaster's case files and through the other rehabilitation centres mentioned above.

4.6.2 Sampling method

We will use a purposive sampling method to balance the groups to include in each group a similar number of participants with regards to the type, cause and length of time since amputation.

[2] An example of the text to be used in the adverts and poster can be seen in appendix E.

The research work is designed to test the effectiveness of the combination of a visual surrogate for the missing limb with haptic feedback (VR + Haptics), as compared with the same therapy without the haptic feedback (VR only). The sample size is based on a priori judgement taking into account the results of recent studies:

- In a recent rubber hand experiment, Ehrsson and colleagues showed that over a single 2hr session, 18 amputees experienced 14% embodiment increase relative to the actual distance between the stump and index finger of the prosthesis (Ehrsson et al, 2008).
- A VR based trial (Murray et al, 2006) with 5 single case studies with similar therapy exposure (7 x 30 min sessions) to our proposed pilot study, reports that the majority of the amputees experienced a pain decrease of 13.3% at the end of the trial (measured by the McGill questionnaire).
- Interestingly, a study inducing proprioceptive feedback mechanisms using functional electrical stimulation, showed a 63% decrease in pain in 5 amputees over a two-week period (Flor et al, 2001).

Taking into account the results of these studies, we expect to observe greater effects with proprioceptive feedback. Thus, for a sample size calculation taken with a probability threshold of .05, anticipated effect .80 with an analysis of variance design expecting a change in the mean pain of 3 points (on the McGill scores) with a standard deviation of 2.3 indicates that a minimum of 20 participants (2 groups of 10) will be needed. Each participant will be receiving the intervention 3 times a week for 3 weeks. Due to technical constraints we estimate that we will be able to run up to 12 sessions a week, thus our maximum capacity will be 60 participants in 15 months.

The proposed number of participants is considered appropriate for an initial evaluation of these therapies for upper limb amputees given the preliminary nature of the work. The purpose of this study is to demonstrate an efficacy of the intervention, not necessarily to quantify it in terms of cost benefit. An interim analysis will be conducted (using the Bootstrap Resampling technique which will give robust standard errors for estimated parameters) to assess the confidence level and if necessary increase the sampling size from 20 participants up to 60 to meet the above statistical power levels.

5. STATISTICS AND DATA ANALYSIS

The biostatistical analysis will be conducted with support from statisticians (Dr Ali Tasiran) in the Design Engineering and Mathematics department, Middlesex University. To assess the homogeneity before treatment of the two groups by age, the type, cause and length of time since amputation and outcome measures, a Mann–Whitney U Test independent samples will be used to compare median scores, whilst the Fisher's Exact Test will be used for frequencies. With regard to interval variables, the two groups will be compared at the end of treatment (difference T1-T0) and at the follow-up (difference T2-T1) using a 2x2 multivariate analysis of variance (mixed MANOVA) in taking into account time of intervention (i.e., baseline and after treatment) and group (VR + Haptics versus VR only). In presence of statistically significant effects, post-hoc comparisons will be performed by comparing the change between T0 and T1, and between T1 and T2 using the Wilcoxon signed rank test and/or by using corrections for multiple comparisons. As regards to the measures provided by AMPSIM system (e.g. kinematic data) a Student t-test will be computed.

It is anticipated that if the hypothesis is supported, significant larger effects (higher pain reduction and increased embodiment levels) will be observed on the VR + Haptics group when compared to the VR only group. This initial analysis will also allow us to observe any temporal effects on pain and embodiment. We estimate a higher temporal effect (e.g. steeper slopes earlier) with the VR + Haptics group. We acknowledge that the effect of novelty (just the fact of someone being involved in the trial) might have an impact on the results. Perhaps if one concentrates hard on something else the pain goes away. It might be insightful to note the transient effects, but what we are fundamentally measuring is the long-term effects. Three weeks might well not be enough to see a substantial effect for all participants (in particular those who have been suffering from chronic Phantom Limb Pain longer). However, if we observe some positive effect at the end of the third week of exposure to the intervention and it disappears at three weeks follow up, then this could drive a longer phase II clinical study or the development of systems that take the elements explored in this study (e.g. the haptics and visualisation) and can be used in people's homes for longer periods.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

6. ETHICAL CONSIDERATIONS and REGULATORY ISSUES

6.1 ETHICS APPROVAL

This study cannot commence without ethics approval from the applicable National Research Ethics Committee. It must be submitted to participating Trust for Site Specific Assessment (SSA). The study will be conducted in accordance with the research governance framework, EU and UK legislations and applicable UK acts.

6.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

6.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study in line with the Data Protection Act 1998.

6.4 SPONSOR

The main sponsor is Middlesex University. The project is MOD funded through Dstl National PhD Scheme, contract No: DSTLX-1000064225.

6.5 FUNDING & COSTS

The MOD through Dstl National PhD Scheme (contract No: DSTLX-1000064225) is funding this study.

Travel costs for the study will be covered for each participant. We appreciate that some participants might be travelling from further afield, thus a maximum amount is not applied.
£400 will be paid to each research site for recruiting to target.
£100 will be paid to the research site for each participant who completed the study.

An Amazon voucher (with a value of £100) will be given to participants at the end of the study for the inconvenience of taking part in the trial.

6.6 MONITORING

Sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

7. PUBLICATION POLICY

The study will be written up and submitted to a peer reviewed academic journal. The results will also be available for internal meetings, to the sponsors of the study and the Aspire CREATe website. If a poster presentation is accepted for a relevant conference, a copy of the poster will be displayed in the Aspire CREATe reception area.

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Participant Number: ……. Session Number: ……. Date/Time:……..

PAIN ASSESSMENT

Level and side of Amputation: ……..... Date of Amputation: ……..……..

Diagnosis: ……..……...……

- What type of prosthesis was supplied? ……..……..……
- Do you have Phantom Sensation or Phantom Pain or Stump Pain? ……
- Are you taking any pain medication: Yes / No
- If Yes, what are you taking (include dosage and when taken)

1. ……..… 4. ……..……
2. ……..… 5. ……..……
3……. 6. ……..……

- How long have you been on this prescription? ……
- How have you found the medication in treating your pain?

Very ineffective 1 2 3 4 5 Very effective

How many days/weeks/years since the operation was performed to remove the limb did the pain begin? ……..

Is your sleep affected? ……..

Name: …….. Sign: …….. Date: ……..

Participant Number: …….. Session Number: ……. Date/Time:……..

Mc GILL PAIN QUESTIONNAIRE

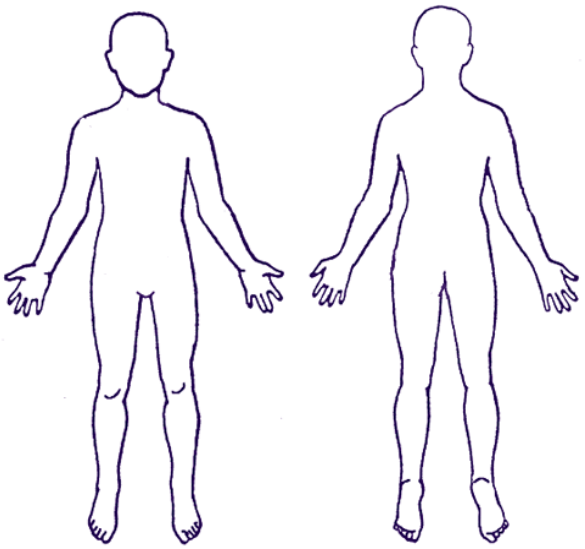
What does your pain feel like?

Some of the words below describe your *present* pain. Circle only those words that best describe it. Leave out any category that is not suitable. Use only a single word in each appropriate category – the one that applies best.

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

Where is your pain?

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



FRONT BACK

Name: …….. Sign: …….. Date: ……..

Participant Number: ……. Session Number: ……. Date/Time:……..

How does the pain change with time?

1. Which word or words would best describe the *pattern* of your pain?

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

2. What kind of things *relieve* your pain? ……...

3. What kind of things *increase* your pain? ……

How strong is your pain?

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

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

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

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

Name: …….. Sign: …….. Date: ……..

Botvinick Questionnaire

Introduction:

The Botvinick Questionnaire was created to gauge the level of embodiment/ownership and effectiveness of the original Rubber Hand Illusion[1]. It has been used in many experiments since the original publication, tailored to the experimental conditions,[2]-[5] to name but a few.

Procedure:

The questionnaire is usually taken in conjunction with proprioceptive drift measurements with the questionnaire always filled after the experiment.

The original questionnaire had a series of 9 statements (listed bellow) to which the subjects indicated their response on a seven-step visual analogue scale ("Strongly Agree +++", "Agree ++", "Slightly Agree +", "Neutral O", "Slightly Disagree –", "Disagree --", Strongly Disagree ---") with the title "During the experiment there were times when:".

- It seemed as if I were feeling the touch of the paintbrush in the location where I saw the rubber hand touched.
- It seemed as though the touch I felt was caused by the paintbrush touching the rubber hand.
- I felt as if the rubber hand were my hand.
- It felt as if my (real) hand were drifting towards the right (towards the rubber hand).
- It seemed as if I might have more than one left hand or arm.
- It seemed as if the touch I was feeling came from somewhere between my own hand and the rubber hand.
- It felt as if my (real) hand were turning "rubbery".
- It appeared (visually) as if the rubber hand were drifting towards the left (towards my hand).
- The rubber hand began to resemble my own (real) hand, in terms of shape, skin tone, freckles or some other visual feature.

AMPSIM:

The procedure for the AMPSIM experiments will be the same as above with different statements to suit the study. These are:

- It seemed as if I was feeling the touch of the objects/environment in the location where I saw the virtual limb touched.
- It seemed as though the touch I felt was caused by the objects/environment touching the virtual limb.
- I felt as if the virtual limb were my limb.
- It felt as if my (real) limb were drifting towards the right/left (towards the virtual limb).

- It seemed as if I might have more than one left/right hand or arm.
- It seemed as if the touch I was feeling came from somewhere between my own limb and the virtual limb.
- It felt as if my (real) limb were the virtual limb
- It appeared (visually) as if the virtual limb were drifting towards the left/right (towards my limb).
- The virtual limb began to resemble my own (real) limb, in terms of shape, skin tone, freckles or some other visual feature.

[1] M. Botvinick and J. Cohen, "Rubber hands' feel'touch that eyes see," *Nature*, 1998.

[2] H. Holle, N. McLatchie, S. Maurer, and J. Ward, "Proprioceptive drift without illusions of ownership for rotated hands in the 'rubber hand illusion' paradigm," *Cognitive Neuroscience*, vol. 2, no. 3, pp. 171–178, Sep. 2011.

[3] L. Schmalzl and H. H. Ehrsson, "Experimental induction of a perceived 'telescoped' limb using a full-body illusion," *Frontiers in human neuroscience*, vol. 5, 2011.

[4] P. D. P. Marasco, K. K. Kim, J. E. J. Colgate, M. A. M. Peshkin, and T. A. T. Kuiken, "Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees.," *Brain*, vol. 134, no. 3, pp. 747–758, Mar. 2011.

[5] C. Preston and R. Newport, "Differential effects of perceived hand location on the disruption of embodiment by apparent physical encroachment of the limb," *Cognitive Neuroscience*, vol. 2, no. 3, pp. 163–170, Sep. 2011.

Illusion Experience Assessment (Botvinick Questionnaire)

Participant Number……. Session Number……..….. Date/Time…….....……

During the session there were times when:

	Strongly Disagree	Disagree	Slightly Disagree	Neutral	Slightly Agree	Agree	Strongly Agree
	---	--	-	o	+	++	+++
It seemed as if I was feeling the touch of the objects/environment in the location where I saw the virtual limb touched.							
It seemed as though the touch I felt was caused by the objects/environment touching the virtual limb.							
I felt as if the virtual limb were my (real) limb.							
It felt as if my (real) limb were drifting towards the right/left (towards the virtual limb).							
It seemed as if I might have more than one left/right hand or arm.							
It seemed as if the touch I was feeling came from somewhere between my own limb and the virtual limb							
It felt as if my (real) limb were the virtual limb							
It appeared (visually) as if the virtual limb were drifting towards the left/right (towards my limb).							
The virtual limb began to resemble my own (real) limb, in terms of shape, skin tone, freckles or some other visual feature.							

Proprioceptive Drift Definition

Introduction:

In traditional rubber hand experiments[1],drift is a measure gauging a distortion of proprioception in participants that typically occurs after exposure to the stimulation. With eyes closed and keeping their left hand in place on the table, participants were asked to indicate the location of their left hand by moving their right hand in a straight line below the table until they feel both hands are in alignment with each other. This task was performed before and after each condition. Drift was calculated by subtracting the pre exposure displacement to the right (i.e., towards the rubber hand) from the postexposure displacement

AMPSIM:

The procedure for taking proprioceptive drift measurements will be similar to that of traditional methods. With the following steps described below:

1. Before (with the HMD on but not displaying anything) & after (again with the HMD on but not displaying anything) the session the participant will keep their amputated limb in place.
2. Using their hand from the residual limb they will indicate the location of their amputated limb by moving their hand in a straight line below the table until they feel both limbs are in alignment with each other.
3. The measurements will be taken and calculated.

[1] W. A. IJsselsteijn, Y. A. W. de Kort, and A. Haans, "Is this my hand I see before me? The rubber hand illusion in reality, virtual reality, and mixed reality," vol. 15, no. 4, p. 22, 2006.

Appendix C

Participant Data

C.1 Short McGill Pain Scores

Participant Short McGill Pain Scores

	Baseline Pain	S1 Pain	S2 Pain	S3 Pain	S4 Pain	S5 Pain	S6 Pain	S7 Pain	S8 Pain	S9 Pain	FU1 Pain	FU2 Pain
P01	2	2.5	2	1.5	1.75	1.5	0.5	1	1	1.5	2	2.5
P02	4	1	1	0	0	0	0	0	0	0	0	0
P03	2.5	2	2.5	1	3.5	3.5	2	4	4	3	2	2
P04	2	3	3	2	3.5	2.5	2.5	3	2.5	2.5	2	2
P05	5	5	4	4	4	2	4	2	2	2	2	3
P06	5	4	2.5	3	3.5	3	3	2.5	3	3	4	4
P07	2.5	2	3	2	2	2.5	2.5	2	2.5	2	1	1
P08	3	1.5	0.5	0.5	2	1.5	0.5	0	0	0	0	1
P09	4	1	0	0	0	0	0	2	0	0	0	0
P10	2.5	0	1	1	1.5	0	0	1.5	0	1.5	1	1
P11	4.5	2	1	1	1	1	0.5	0.5	0.5	0.5	0.75	1.5
P12	1.5	1.5	1	2	2	2.75	1.5	1	0.5	1	1.5	1

C.2 Embodiment Questionnaires

P01

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	2	5	5	5	1	5	5	1	5
2	5	5	5	1	1	5	5	1	5
3	4	4	5	1	1	5	5	1	3
4	4	4	6	1	1	7	6	1	6
5	5	5	6	1	1	6	7	1	7
6	7	7	7	1	1	7	7	1	7
7	7	7	7	1	1	3	7	3	7
8	7	7	7	1	1	6	7	1	7
9	7	7	7	1	1	7	7	1	7

P02

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	6	6	7	7	1	2	7	6	6
2	6	1	6	5	1	1	6	5	6
3	6	3	6	5	1	2	5	5	6
4	7	2	6	3	1	6	7	2	6
5	6	3	7	2	1	5	7	3	6
6	7	4	7	2	1	2	7	2	6
7	7	2	7	5	1	2	7	3	6
8	7	1	7	2	1	2	7	2	6
9	6	2	7	2	1	5	7	1	6

P03

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	7	4	1	1	1	1	1	1	1
2	4	4	2	2	2	1	4	6	2
3	2	2	2	6	2	2	2	6	1
4	1	1	2	2	2	1	2	2	1
5	1	1	1	1	1	1	1	1	1
6	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1
8	1	1	1	1	1	1	1	1	1
9	1	1	1	1	1	1	1	1	1

P04

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	1	1	6	2	1	5	5	1	2
2	2	2	5	2	4	1	5	5	3
3	2	2	5	2	2	2	5	2	2
4	2	2	3	2	2	5	4	2	2
5	2	2	2	4	3	5	4	4	2
6	2	2	5	2	2	4	4	2	5
7	2	2	4	2	2	2	5	2	4
8	4	4	4	2	2	2	4	2	4
9	3	3	3	2	2	2	4	2	4

P05

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	2	2	7	1	1	1	7	1	6
2	6	6	7	2	1	2	7	2	6
3	6	6	7	1	1	2	7	2	6
4	7	7	7	1	1	2	7	1	6
5	6	6	6	2	1	2	6	2	6
6	7	7	7	2	1	1	6	2	6
7	7	7	7	2	1	4	7	1	7
8	7	7	7	2	1	2	7	1	6
9			7						

P06

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	5	5	2	2	2	2	2	2	1
2	4	4	5	2	2	4	5	2	1
3	2	2	4	2	2	2	4	2	1
4	2	2	4	2	2	2	4	2	1
5	2	2	4	2	2	2	4	2	1
6	2	2	2	2	2	2	2	2	1
7	2	2	4	2	2	2	4	2	1
8	2	2	4	2	2	2	4	2	1
9	2	2	4	2	2	2	4	2	1

P07

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	2	2	5	2	1	2	5	2	4
2	5	5	3	2	2	6	3	2	2
3	5	5	3	2	2	2	2	2	2
4	6	6	4	2	2	3	4	2	4
5	6	6	5	2	2	3	5	2	2
6	6	6	5	2	2	6	5	2	3
7	6	6	5	2	2	6	5	2	5
8	6	6	5	2	2	2	5	2	4
9	6	6	6	1	1	6	6	1	5

P08

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	2	2	5	2	1	3	7	1	1
2	5	5	6	3	1	6	6	5	1
3	4	4	6	3	1	6	7	1	3
4	6	6	5	1	1	6	7	1	5
5	7	7	7	2	1	6	7	2	3
6	6	6	6	2	1	1	6	1	6
7	7	7	7	4	1	1	7	4	7
8	7	7	7	1	1	1	7	1	7
9	7	1	7	1	1	1	7	2	7

P09

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	7	7	7	5	3	5	7	5	6
2	6	6	6	5	1	2	6	2	6
3	6	6	6	2	2	2	6	2	6
4	7	7	6	2	2	6	2	2	6
5	6	6	5	2	2	2	6	2	5
6	7	7	7	2	2	6	6	2	6
7	6	6	5	2	2	3	6	2	5
8	7	7	6	2	2	2	7	2	6
9	7	7	7	1	1	6	7	2	7

P10

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	2	2	7	2	2	2	7	3	6
2	3	5	7	1	1	2	7	2	6
3	6	6	6	5	2	2	7	2	6
4	3	6	6	2	1	2	7	2	6
5	6	6	7	5	1	1	7	5	7
6	6	6	7	2	1	1	7	1	6
7	6	6	6	5	2	2	6	5	6
8	6	6	7	2	1	2	6	3	6
9	6	6	7	2	2	2	6	2	6

P11

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	4	4	5	2	2	5	6	2	6
2	5	5	5	2	2	5	5	2	5
3	5	5	5	2	3	5	2	2	5
4	5	5	5	2	4	5	4	2	5
5	5	5	5	3	5	5	5	2	5
6	5	5	5	2	5	5	5	2	5
7	6	6	5	2	5	5	6	2	6
8	6	6	6	2	5	6	5	2	6
9	6	6	5	2	6	6	5	2	6

P12

Session	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	2	1	5	5	6	5	1	6	1
2	3	2	5	4	4	5	2	2	1
3	2	3	2	1	5	5	2	2	1
4	3	4	3	1	4	5	5	6	1
5	5	5	3	3	4	5	4	5	1
6	5	4	2	5	6	6	4	6	1
7	5	5	5	6	6	6	5	2	1
8	5	4	5	5	4	6	5	4	1
9	5	5	5	5	6	5	5	4	1

C.3 Proprioceptive Drift Measures

P01

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	56	24	66.2	27.5	65	20	69.8	26.5
2	55	20.7	64.5	20.7	62	24.5	55.3	24.5
3	66.8	20.9	68.7	21.2	66.2	22.5	67.4	22.5
4	66	21.3	65.8	20.3	69.8	24.5	59.5	23.6
5	68.7	18.6	63.9	20	69.6	20	53.8	21.7
6	75	18.6	63	32.5	71	17	66.1	24.4
7	73.6	20.7	69.8	29.2	78.1	24.5	74.9	24.5
8	66	16.4	65.9	28.3	78.5	19.8	75	20
9	76.1	16.4	65.3	18.5	81.5	22.5	72.8	27.2

P02

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	51	27.5	58	26	51	27.5	57	27.7
2	59.2	21.7	51.7	22.5	69.2	20.2	61.8	25
3	63.5	23.5	56.6	23.6	64	22	61.2	24.4
4	50.2	20.2	51.4	21.9	62.6	21	57.6	24.5
5	57.4	24.4	53.9	26.7	57.6	21.5	60.1	23.5
6	61	16.1	56.9	23.7	62.8	24	58	23.5
7	55.3	21.3	56.4	21.3	53.8	21.2	45.5	21.3
8	58.7	22	56.6	24.3	59.8	27	46.5	26.3
9	58	25.4	51.9	27	52.3	26.4	42.3	26.9

P03

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	47.3	29	64.4	36.7	34.4	30.7	38.7	25.3
2	35.5	37.7	35.8	26.6	56.3	31.7	61.9	25.7
3	34.8	27	36.4	9.1	41.3	35	29.9	16.3
4	33.1	27	33.1	2.9	31.7	30.4	29.8	19
5	36.2	29	31	9	35	30.6	29.9	15.8
6	33.1	23	31.5	1	30.7	36.5	30	21.5
7	34.8	30.6	30.6	12	31.8	30.4	35.4	12.6
8	32.5	48.7	25.5	22	37.7	38.2	41.4	21.2
9	37.4	32.3	24.5	10	35.5	40.5	25.5	16

P04

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	32.3	19.5	38.8	5	27.4	26	25	16
2	27.2	18	33.1	13	30.4	22.5	36.6	14.6
3	28.5	19.7	31.8	5.5	27.5	19.4	34	7.5
4	28.2	19.5	35	12.7	30.1	34.2	33.7	18
5	28	18.1	37.2	5	28	21.5	41.2	5
6	27.8	20.7	36	10.7	26	11.6	44.5	8.4
7	32.8	9.6	36.5	3.5	31.5	17.7	42.4	5.2
8	32.8	12	40	4.8	37.4	18.5	41	15.2
9	35	16.8	42.5	6	33.6	19	43.3	8.8

P05

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	39.7	16.6	46.2	20.9	55.6	19.7	53.4	22.3
2	44	17.2	51.6	21.7	56	16.1	48.5	18.8
3	49.5	21.9	46.9	15	55.5	17.2	58.4	19.7
4	58.5	20	47	17	56.5	16.5	54	26.5
5	51.5	16.5	53.9	22.5	57.5	16	55	17.5
6	49	15.5	53.5	19.9	57.3	17	53.8	16.5
7	52.5	22.9	46.5	11.5	55	22.6	47.6	28.5
8	52.5	17	49.2	16	60.5	15.3	55	18.4
9								

P06

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	56.5	35	59	19	36.5	24	44	18.5
2	62.5	32.4	57.3	18.4	42	33	50	24.9
3	56.5	30.5	56	20	46.5	31.2	54	23
4	60.2	32	60.1	17.5	47	39.5	51	27.7
5	55.5	31.16	57.2	18.8	48	35	51	27.7
6	60.2	36	60.8	27.1	42.3	35.6	46	25.5
7	51.5	31	51	18.2	46.5	31.5	50.6	21.5
8	56.6	33.8	56.5	23	48	39.1	47.9	30.2
9	55.3	32.5	54.1	17.6	50.9	38.6	49.2	30.8

P07

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	47.5	16.4	55.2	17.6	39.9	22.3	47	15.7
2	41	13.9	33.2	17.2	36	29.7	30.6	29.4
3	27	11.9	24.2	15.6	31.5	23.5	40.4	25.6
4	39	11.3	31.5	17.7	39.8	23.5	54.7	27.2
5	25.8	21.4	25.6	22.5	28.5	19.6	30.2	24.5
6	33.6	23.8	31.4	24.2	35.4	15.3	30	20.2
7	34.4	15.2	36	23.7	36.4	14	31	15.7
8	31.9	21.1	30.1	21.1	38	15.5	35.8	16
9	28.5	12	33.1	17.5	35.6	13.7	30.2	15.7

P08

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	43.2	36	43.2	34.5	32.5	36	35.2	28.3
2	43.5	38	43	30.2	43.5	38	44	22.2
3	53.4	36	46.4	28.5	42	32	46	27.5
4	44.6	36	46.6	29.1	48.6	34.2	68	23.2
5	42.2	33.6	44.8	23.7	38.5	33.3	45.5	22.9
6	45	33.5	47.2	20.7	40.5	36	45.5	30.9
7	43.5	34.4	47.4	32.1	47	35.5	51.9	29
8	41.5	33.2	46	24	44.9	32.3	54.5	23.7
9	42.9	33	36.9	28.5	48.9	34.2	47.6	35.5

P09

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	44	37	39.7	30.2	44	35	33	28.5
2	36	32	29.4	25.4	44.2	28.1	32.1	28
3	32.2	22	26	24.2	34.2	26.5	26.3	25.4
4	36.5	24.8	31.7	24.6	38.5	33.5	33	31.5
5	34.2	34.2	28.1	26	35.5	34.4	29	25.9
6	29.5	31.2	24.1	23.9	45.4	39	32.9	30
7	40	31.4	32.4	27	45.7	39	37.3	30.7
8	36.7	36.2	29	27.6	33.6	33	24	19.2
9	36.2	34.5	31	27	38.2	35.5	32.5	24.5

P10

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	33	21.6	31.2	27.4	34.4	27.7	34.4	29.4
2	23.2	22	30.1	35.5	31	25.9	33	30
3	29.6	20.3	33.4	31.4	27.9	24.2	29.4	25.7
4	31.8	15.3	38	19.8	28.5	23.6	34.5	24.5
5	26.7	17.9	27.4	21.4	31.5	20	42.3	27.6
6	30.2	11	33.2	15.5	37.7	27	34.9	28
7	32.3	16	38.5	26.8	28.1	28	31.7	28.4
8	35.5	24.5	42.2	25.6	33.9	24.7	46.1	28.5
9	29.5	26	42.1	27.5	33.2	27.1	46.2	30.2

P11

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	38.8	22.1	42.3	11.5	40.9	25.9	43.2	2
2	31.7	31.8	39.6	16.5	32.2	30.9	40.9	16.5
3	35.4	35.2	44.8	16	29.5	28.3	41.2	7.6
4	35.4	24.5	39.9	8.2	33.8	26.8	46	12.6
5	36.6	30.3	40.4	14	36.6	30.2	43.6	13.2
6	38.7	35.3	43.6	18.3	36.6	28.7	46	10.2
7	42	30.7	45.5	10.2	34	23.2	43.7	3.9
8	31	30	39.3	12.5	35.6	25	47.6	7.6
9	24.7	30.2	38.4	14.5	27.7	20.5	39	2.1

P12

	cm	cm	cm	cm	cm	cm	cm	cm
Session	**Ref Pre X**	**Ref Pre Y**	**Pre X**	**Pre Y**	**Ref Post X**	**Ref Post Y**	**Post X**	**Post Y**
1	34	14.2	34	0	40	15.3	36.7	0
2	36.5	15	29	0	41.1	15.6	30.5	0
3	34.9	24.5	36.5	1.5	37.4	24.3	19.9	0.5
4	32	13.5	37	0	38.5	14.2	45	0
5	29.6	13.8	31.1	0	27.2	19	37.5	0
6	30.4	10.9	30.4	0	49.2	8.8	34	0
7	32.5	15.6	31.5	0	30	9.8	24.5	0
8	29.7	17.7	31.7	-11	28.2	21.8	34.5	4.6
9	22.3	5.3	25	24	27	23.6	31	7

Appendix D

Additional Technical Data

D.1 System Design

D.1.1 OpenVibe

OpenVibe, initially a Brain Control Interface (BCI) software was developed in collaboration with Inria Rennes and partners, comprised of two parts, an acquisition server and a programme designer. Due to OpenVibe's open source nature the software is ever evolving both in devices supported and features available to the user when designing programmes.

The acquisition server allows connection to a vast and growing range of acquisition devices such as g.tec, Brain products, OpenEEG and TMSi devices to name but a few. The open source nature also allows users to write drivers for acquisition devices not yet supported. The communication protocol such as USB, Bluetooth or WiFi can be selected as well as the sampling frequency and sample count per sent block from the device to the OpenVibe designer.

The OpenVibe designer is used to programme custom made software to access the raw data from the acquisition server and to process the data to perform such tasks as classifying signals etc.

Example usage of the OpenVibe designer can been seen in Figure D.1. Similar to UE4 flow box visual programming is used with different coloured arrows as input/output on the boxes corresponding to different elements within the data such as streamed values, triggers, participant information. Boxes provided by the designer act as function box such as timers, filters, classifiers etc. The collection of these make up the user made programmes.

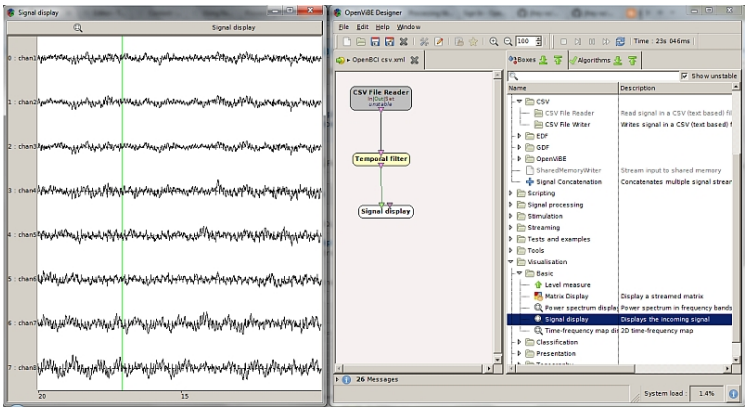


Figure D.1: Sample screenshot from the OpenVibe Designer. Showing reading of a csv file and the resulting output in real time.

OpenVibe was used to:

1. Initially collect grasp/release data using the Graz Motor Imagery test.
2. To classify the grasp/release data to produce a classifier file.
3. To perform online classification of the participant's EMG data during the sessions, sending not just the output (binary value) of the classifier but streaming the raw data of all the signals (EMG/GSR/Respiration) and saving a backup copy of this raw data session wise.

Which can be summarised in Figure D.2.

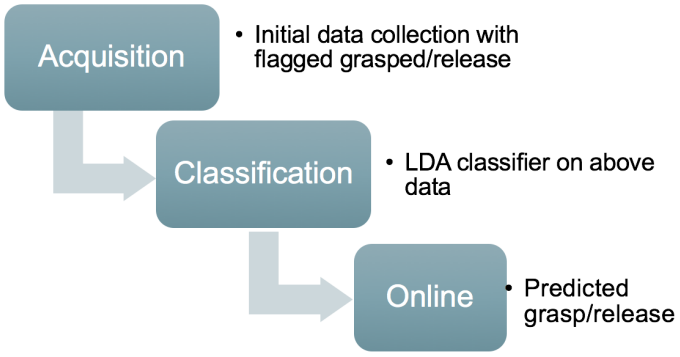


Figure D.2: Flow diagram showing the steps required to classify EMG signals for grasp/release within OpenVibe.

Three files were produced to achieve these three activities. The first two files were run at the baseline session and when the accuracy for the classified grasp/release needs to be improved during the session, with the final file being run at the start of each session.

The first file is responsible for collecting raw data during the Graz Motor Imagery task in which 20 arrows are randomly displayed pointing either left or right for 4 seconds before

a blank screen is shown for 6 seconds. The participant is told when they see an arrow pointing left to relax and when it points right to perform a grasp. The raw data is saved to be used in the next step.

This involves running the raw labelled data through a classifier which results in a classifier that produces a classifier file to be used in the final file.

The final file 'online.xml' first establishes communication to the acquisition device then splits the channels. This is achieved by using VRPN or Virtual Reality Peripheral Network. A protocol allowing device independent data to be sent via network created by Taylor et al in 2001 [206]. Channel 27 (Bipolar) is first segregated to have the classifier applied to channel 27's raw data stream after which the raw data stream is sent to a VRPN analog client box to be sent to UE4 along with the result of the classifier (either grasp or release) being sent to an VRPN button (binary) client. The other channels used 28 and 29 (Bipolar) are used respectively for GSR and Respiration data. Like the EMG data these two channels send their raw data streams via VRPN to UE4 in separate VRPN analog clients. A total of three VRPN analog clients are used and one VRPN button client. To aid backup of the data from the acquisition device all used channels (27-29) have their raw data streams logged to a csv file using the csv writer box. This saves one file per session per participant.

D.1.2 Oculus Rift

The main benefit of the Oculus Rift and the reason why it's impact has been so great could be seen due to it's simplistic design and development at a time at which the technologies it employees were available to the mass market. Figure D.3 provides a simplistic overview and breakdown of the main components that make up the Oculus Rift also highlighting the 3 main components of the headset; lenses, the display and the head tracking.

Figure D.3: Breakdown of the Oculus Rift DK2 headset with numbered parts highlighting the main components of the headset

1. Lenses Establishing a focal point is critical to perceiving depth. In essence, the user's eyes are staring beyond the display and into the virtual environment. Initially the Oculus Rift DK1 came with 3 lenses to accommodate those users who require glasses via dioptric correction before being replaced by Fresnel lenses along with a focus adjustment slider. Fresnel lenses are thiner and provide greater focus than the original lenses found in the development kit 1 version of the Oculus Rift.

2. Display A high-resolution screen that sits just a few inches from a user's eyes projects a stereoscopic image or two warped images on each half of the screen, similar to the concept of humans using binoculars with added horizontal offsets between objects visible in the left and right eyes, which the visual cortex can process to perceive depth. Ineffectively using 2D virtual objects which when viewed in close proximity to the user whilst wearing the headset tricks the brain into thinking the objects are in a virtual environment with depth, aka a 3D environment.

3.Tracking Technology The original DK1 Oculus Rift headset came equipped with various sensor inputs, e.g. a gyroscope, accelerometer, and compass track the location of a user's head position and orientation as seen in Figure D.4.

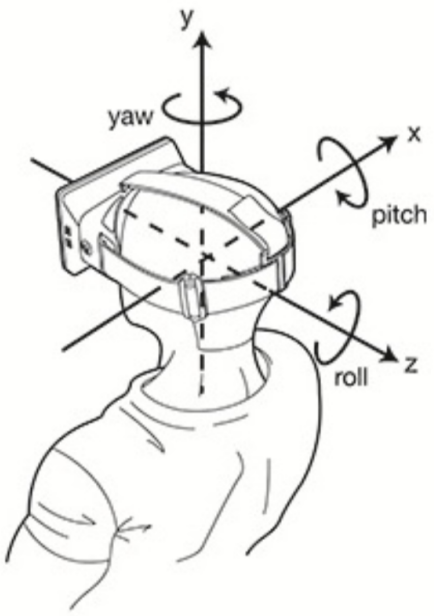


Figure D.4: The orientation axis of the Oculus Rift DK1 Headset. Extracted from LaValle et al [226]

The original Oculus Rift (DK1) was sold in 2013, utilising a single 7 inch tablet screen, and an external box to which connections to the PC were made. The second development kit (DK2) version utilised two separate tablet screens one for each eye and removed the external box opting for a straight connection to the PC, however both the camera and headset had to be synchronised via USB before being sent to the PC. The most up to date version of the Oculus Rift (CV1) as shown in Figure D.5 uses as similar to the DK2 two separate displays for each eye however a much higher refresh rate is used (90Hz) and higher display resolution (1080 x 1200 pixels) than previous models and field of view (110 degrees as opposed to 90 degrees in the DK1) along with integrated audio.

Figure D.5: The Oculus Rift CV1 with HMD tracking infra red camera

The addition of an external camera does provide further initial set up using the Oculus Home application however once this is completed the data is passed seamlessly into Unreal Engine. The tracking area of the CV1 version of the Oculus Rift is 5 foot square, enough for the purposes of the research. This is due to the table/tripod mounted nature of the camera. Other manufactures of 3D headsets such as the HTC Vive use wall mounted cameras thus providing 15 foot square tracking area, however due to the portability of the Oculus system the smaller tracking area is more beneficial rather than the whole room tracking the HTC Vive uses which is more suited for systems that allow free movement around a room.

Integration within Unreal Engine is natively supported. A virtual "camera" which consists of the position and orientation derived directly from the headset. This camera is then placed within the head of the virtual avatar. In the case for left handed exercises an off-set is applied to the orientation of the headset since the environmental objects around the user (e.g not the objects to be manipulated) stay in the same position.

D.1.3 Gimbal

The potmeter have to be calibrated to zero to ensure correct Euler axis conversion. Calibration is achieved via a web interface and ensuring the potmeters (apart from potmeter 3 due to the physical construction).

Euler axis conversion is performed at the Unreal Engine 4 plugin level in which first the values of the three potmeters are polled. The process can be broken down into three steps:

1. The output of each potmeter has to be retrieved from the HapticMaster server (in radians) and assign each value to an array.
2. These values in the array are then converted into yaw-pitch-roll values (in degrees).
3. The values are then sent via a plugin to Unreal Engine 4 and transformed depending on if the exercises are being carried out by a left or right handed amputee participant.

In order to correctly provide the inverse kinematic algorithm with the correct values for $\boldsymbol{q}_e$ data has to be collected from the 3 potmeters located on the gimbal and transformed into values suitable to be applied to $\boldsymbol{q}_e$. This next section will detail how this is performed.

The axis going vertically (attached to the end of the HapticMaster) provides the yaw movement of the gimbal and uses potmeter 3 (defined by the HapticMaster API). The second axis going down the gimbal provides pitch to the gimbal and uses potmeter 1. The last axis on the gimbal provides roll and uses potmeter 2. Yaw-Pitch-Roll user axes are used by Moog which is the tradition euler axes definition, after which the three axes have to be converted into a quaternion to satisfy $\boldsymbol{q}_e$. Preferably the potmeters have to be correctly calibrated and zeroed regularly.

To transform from potmeter angles to yaw-pitch-roll angles quaternions are used in the two step process as follows:

1. Derive the attitude quaternion from the potmeter angles. The quaternion produced represents gimbal axis rotations in user coordinate components.
2. Transform this quaternion into user yaw-pitch-roll axes.

Quaternions are used due to the fact that they represent an altitude in space relative to a fix coordinate frame. These quaternions are multiplied to transform the original quaternion by one or many successive rotations. The attitude quaternions mentioned above are rotated relative to a fixed frame by multiplying with a rotation quaternion in that fixed frame. As a result part of the process involves defining rotations from each fixed framed axes (defined above, the potmeter readings for yaw-pitch-roll). The final quaternion used is a product of the rotations of the potmeters angles in a fixed frame. E.g:

$$q = q1 * q2 * q3 \tag{D.1}$$

Where q is the final quaternion and are potmeter rotations of the 3 axes. With q defined as:

$$q = [e_1.sin(\frac{1}{2}\phi)e_2.sin(\frac{1}{2}\phi)e_3.sin(\frac{1}{2}\phi)cos(\frac{1}{2}\phi)] \tag{D.2}$$

With $\underline{\mathbf{e}}$ as the unit vector axis, one per potmeter axis and ϕ being the angle of that potmeter.

To find firstly the gimbal axis unit vectors have to be defined in their original fixed frame (e.g default/zeroed position) adding the angles into the above equation.

In the default position the XYZ axes can be defined via the gimbal to produce the user frame. The 3 axes can be defined as:

$$axis1 = [\quad 0 \quad 0 \quad 1 \quad] \tag{D.3}$$

$$axis2 = [\quad -sqrt(\frac{1}{2}) \quad -sqrt(\frac{1}{2}) \quad 0 \quad] \tag{D.4}$$

$$axis3 = [\quad +sqrt(\frac{1}{2}) \quad -sqrt(\frac{1}{2}) \quad 0 \quad] \tag{D.5}$$

Once the measured potmeter reading have been factored the 3 rotations can be derived to yield the final quaternion to be used to find the yaw-pitch-roll below:

$$tan(yaw) = 2(q_0q_1 + q_3q_2)/(q_3^2 + q_0^2 - q_1^2 - q_2^2) \tag{D.6}$$

$$sin(pitch) = -2(q_0q_2 - q_3q_1) \tag{D.7}$$

$$tan(roll) = 2(q_3q_0 + q_1q2)/(q_3^2 + q_0^2 - q_1^2 - q_2^2) \tag{D.8}$$

The yaw/pitch/roll is now sent to the IK layer found in the animation blueprint in Unreal Engine 4.

D.1.4 Classifier for EMG

D.1.4.1 Linear Discriminant Analysis

In essence the aim of Linear Discriminant Analysis (LDA) is to project the original data in the form of a matrix onto a lower dimensional space, similar to Principal Component Analysis (PCA), with PCA being used for unsupervised data with the aim of maximising the variance within a given dataset, and LDA focusing on maximising the separation between multiple classes (in our case two) in order to provide classification.

LDA's use vectors in order to separate the data set into the required classes.

An example of a two case LDA can be seen in Figure D.6. the class of a feature vector

depends on which side of the vector it lies. With two classes circles and triangles are separated by the equation $w_0 + w^T x = 0$. If the calculation of the vector to be tested during classification is greater than 0 it is therefore classified as a circle otherwise a triangle.

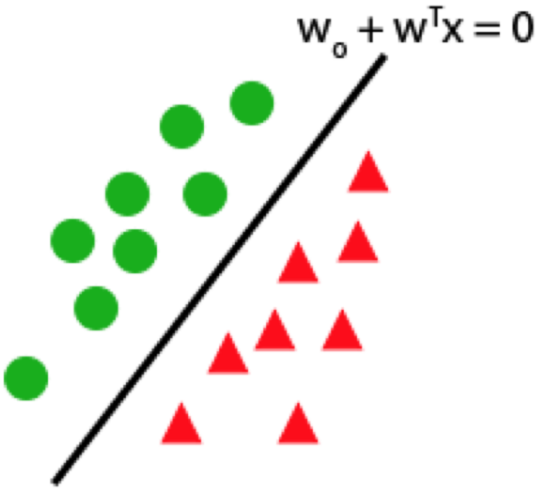


Figure D.6: A over simplified example of an LDA

LDA classifiers enforce a normal distribution for the data used in the classifier for both classes and the separating vector is obtained by searching the line that maximises the distance between the two classes means, with the minimum variance. The LDA classifier is generally simple to implement and due to the low number of classes the classifier is generally used for provides robust classification. A mathematical overview of an LDA is detailed below:

Given a function $f_K(x)$ that states conditional probability that a point within data with a number of features x is associated with a specific class $C = k$ and that π_k denotes the probability that any one of these classes will exist satisfying:

$$\Sigma_k \pi_k = 1 \tag{D.9}$$

Predictions can then be derived by using Baye's theorem model to the class conditional distribution of the data with this information:

$$P = (C = k | X = x) = \frac{f_k(x)\pi_k}{\Sigma_k f_k(x)\pi_k} \tag{D.10}$$

However the above assumes that all of the classes have a common covariance matrix satisfying:

$$\Sigma_k = \Sigma_k \forall k \tag{D.11}$$

In addition, it is assumed that classes are distributed as multivariate Gaussian distributions.

With this information logistic regression can be used to transform the probability above into log odds of the two classes, this is achieved by finding the odds ratio product and taking the log value of that product:

$$\begin{aligned} log\frac{P(C=k|X=x)}{P(C=l|X=x)} = log\frac{f_k(x)}{f_k(x)} + log\frac{\pi_k}{\pi_l} \\ = log\frac{\pi_k}{\pi_l} - \frac{1}{2}(\mu_k+\mu_l)^T\sum^{-1}(\mu_k-\mu_l) + x^T\sum^{-1}(\mu_k-\mu_l) \end{aligned} \tag{D.12}$$

The above equation provides the log-odds between any two classes as a linear function, which in turn ensures that the decision boundary between any k and l means there is a probability of a data point being in either class equivalent to 50% also being linear in fashion too. As a result this gives us a linear hyperplane as seen in Figure D.6 providing a solution of:

$$G(x) = argmax_k\left(\delta_k(x) = x^T\sum^{-1}\mu_k - \frac{1}{2}\mu_k^T\sum^{-1}\mu_k + log\mu_k\right) \tag{D.13}$$

with the above being solved by gradient descent.

Given a sequence of points y_i, and a sequence of points predicted by a model $\hat{y}_i$ the residual sum of squares is:

$$error_(m,b) = \sum_{i=1}^{n}(y_i - \hat{y}_i) \tag{D.14}$$

Minimising the error via using values for the $\hat{y}_i$ predictions turns the above equation into the below, where b is the intercept and m is the slope of the line of best fit:

$$ResidualSumSquares(RSS) = \sum_{i=1}^{n}(y_i(mx_i+b))^2 \tag{D.15}$$

with the gradient being derived from a set of two partial derivatives:

$$\left\langle \frac{\delta}{\delta b}(RSS), \frac{\delta}{\delta m}(RSS) \right\rangle = \left\langle -2\sum_{i=1}^{n}(y_i-(mx_i+b)), -2\sum_{i=1}^{n}x_i(y_i-(mx_i+b)) \right\rangle \tag{D.16}$$

In order to solve the above equation on each execution a step in the negative gradient direction is performed, resulting in convergence.

The above provides a simple overview of the LDA classifier.

D.1.4.2 k-fold test

The K-fold cross validation method generally gives better estimation results than just a native testing. This method consists on dividing the set of feature vectors in a number of partitions and train the classification algorithm on some of the partitions, and its accuracy is tested on the others. Due to the simple nature of the EMG classification, k-fold cross validation was used with a low parameter value.

D.1.5 Control Theory

A core aspect in robotics is how the robot interacts within its environment. Implementing any control technique will involve the use of force in order to position the robot within a desired position taking into consideration external elements such as the resistance from a user/environment.

Control of these forces is a priority for the system as a whole to function. In order to achieve this control elements such as task modelling the environment, position, velocity and force feedback, and adjustment of the applied torque to the robot joints are required, along with feedback from various sensors such as the output of a robot (position, force, velocity) and human input which result in different force control methods [227].

Impedance/Admittance control along with hybrid controls are seen as traditional algorithms based on the application of their relationship between position and applied force or between velocity and applied force, or the application of direct force feedback, or their combinations [227].

Fundamental in force control is how to dictate the external interaction forces and implement the feedback signals in order to produce the correct input signals, so that the desired motion and force of the robot can be maintained. Position, velocity, acceleration and force are core variables needed in order to achieve force control.

D.1.5.1 Stiffness Control

Before discussing Impedance and Admittance control; Stiffness control needs to be examined which will enable discussing additions to the algorithm which make up the other control methods.

Stiffness control can be passive or active. In passive stiffness control, the end-effector of

a robot arm is equipped with a mechanical device composed of springs/dampers to create an open-loop system. Active stiffness (Figure D.7) control can be regarded as a programmable spring, since through a force feedback the stiffness of the closed-loop system is altered.

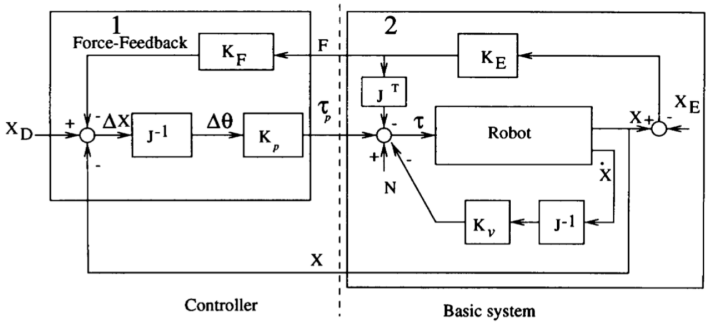


Figure D.7: Basic principle of an active stiffness control. Extracted from [227]

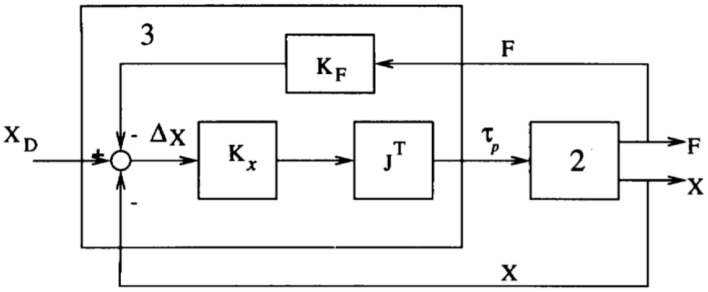


Figure D.8: Basic principle of an active stiffness control 2. Extracted from [227]

For better understanding, Figure D.7 is divided into two parts : the controller part, denoted as box 1 and the basic system, denoted as box 2. The basic system includes a robot and its environment, velocity feedback and nonlinear compensation for linearising the robot dynamic system. The stiffness control loop comprising a proportional feedback of force and position in box 1 defines joint torque τ_p of the total joint torque τ due to the contact force.τ_p is thus defined by the following equation:

$$\tau_p = J^T K_x \Delta X \tag{D.17}$$

where $K_x$represents the stiffness matrix. Since $\Delta X = J\Delta\theta$, then $\tau_p = J^T K_x \Delta\theta$ That means:

$$K_p = J^T K_x J \tag{D.18}$$

D.1.5.2 Impedance control

Hogan in 1985 [228] laid down the framework for impedance control. Stating that "the manipulator control system should be designed not to track a motion trajectory alone, but

rather to regulate the mechanical impedance of the manipulator" [228]. The relationship between the velocity $\dot{X}$ and the applied force F is referred to as the mechanical impedance denoted as Z_m. If relating this relationship in a frequency domain rather than a time domain, then the relationship can be modelled as:

$$\frac{F(s)}{\dot{X}(s)} = Z_m(s) \tag{D.19}$$

In terms of position $X(s)$, the above can be modified giving us:

$$\frac{F(s)}{\dot{X}(s)} = sZ_m(s) \tag{D.20}$$

Simplifying the position in a linear fashion the selected impedance required can be modelled as:

$$sZ_m(s) = Ms^2 + Ds + K \tag{D.21}$$

Figure D.9 demonstrates the overview of impedance control showing the control loop which calculates a suitable value for $Z_m(s)$

Both Figure D.9 and Figure D.7 are similar. What Figure D.9 adds is an extra feedback loop for the addition of both velocity and the effect of the contact force on the velocity. Impedance control therefore can be seen as a proportional and derivative controller in which the provided forces results into amendments in the system for the correct for position and velocity. Amendments to the position results from multiplying the provided forces by a matrix K_F1 which acts as stiffness control as seen in D.7. Velocity in impedance control is modified by multiplying the provided forces by a matrix K_F2. In the joint space the command force for error correction, thus, is defined by:

$$\tau_p v = J^T (K_p \Delta X + K_v \Delta \dot{X}) \tag{D.22}$$

In addition D.9, box 4.2 houses the control loop which is responsible for modifying the damping constant of the manipulator when it is in contact with the environment. As such Impedance control is normally implemented when a robot is requires to adapt to any damping in it's external environment.

Impedance control can be further enhanced (Figure D.10), in which X_F represents the

equivalent force-feedback trajectory output, X_I represents the modified desired trajectory derived from the equation below, where $X_I(0) = X_D(0), \dot{X}_I(0) = \dot{X}_D(0)$. M,D&K and who's values have been previously defined:

$$M\ddot{X}_I + D\dot{X}_I + KX_I = -F + M\ddot{X}_D + D\dot{X}_D + KX_D \tag{D.23}$$

The above equation can been derived from Figure D.10 and also implies the same equations as the position relationship and linear impedance (as seen above). The impedance control formulation X_I is a function of both the input X_D and the measured contact force F. Since the position-controlled subsystem in box 5 of Figure D.10 it therefore ensures that the end-effector position X closely tracks X_I defined in equation above, ensuring that the target impedance of the manipulator is obtained.

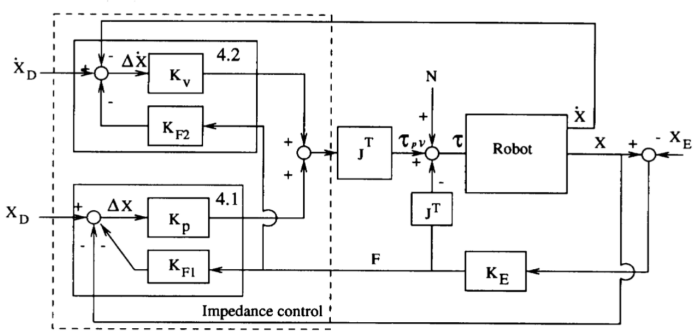


Figure D.9: Basic impedance control model. Extracted from [227]

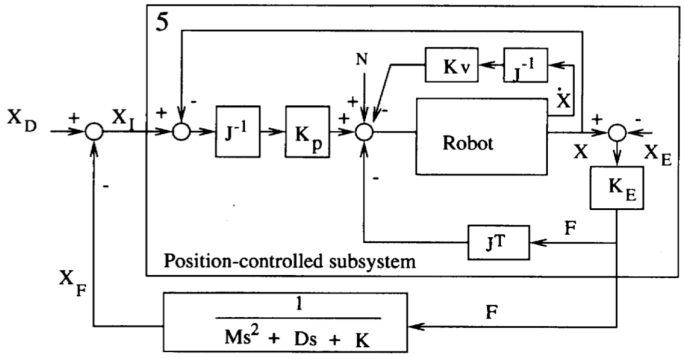


Figure D.10: Position-based impedance control model. Extracted from [227]

D.1.5.3 Admittance control

Mechanical admittance in a system is clearly stated as:

$$A = \frac{\dot{X}}{F} \tag{D.24}$$

The above equation is the direct inverse of the impedance equation for position in the section above. Figure D.11 provides a simple overview of admittance control.

Within Figure D.11, the admittance matrix A relates the force error vector $E(E=F_D-F)$ to the end-effector velocity perturbation. For a known environmental stiffness, an admittance A can be solved to achieve a desired force response with small or zero error, low overshoot and rapid rise time. The command trajectory X_c is defined as:

$$X_c = \int A(F_D - F)dt \tag{D.25}$$

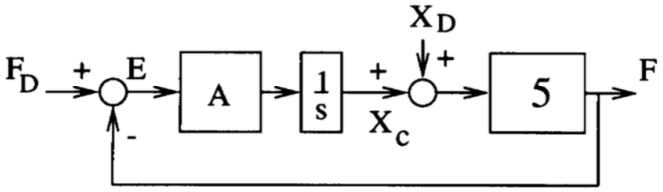


Figure D.11: Admittance control model. Extracted from [227]

To expand the definition of admittance, with respect to the knowledge that admittance is the inverse of impedance. Another main difference in admittance control over impedance control is where forces are applied, either through open-loop or closed-loop control, to the human user after motion is detected. The underlying concept of compliant motion control using admittance is to take a position-controlled robot as a baseline system and to make the necessary modifications of the admittance to this system in order to enable the execution of constrained tasks. To compare with impedance control, admittance control focuses more on desired force tracking control. Admittance controlled devices excel in rendering stiff virtual surfaces however struggle to render low inertia. Due to element of difficulty in dynamically interacting with stiff real surfaces via constrained motion [229]. The impedance control systems inversely excel in rendering low inertia but struggle to render stiff virtual surfaces. The issue here arise by dynamically interacting with low inertia via free motion [229].

A schematic admittance controlled device is shown in Figure D.12. An actuator generates mechanical power by the supply of electrical power through a controlled current or applied voltage. Such an actuator is commonly an electromechanical motor. These actuators usually impose forces on the mechanics of the device, which consists of a drive train, moving parts and robotic links. Close to the interaction point a force sensor measures the interaction

forces with the user. This sensor is usually non-collocated with the actuator.

A force sensor has non-zero inertia, and usually a tool (for industrial applications), handle (for manual interaction) or cuff (for exoskeleton-like applications) or in the case of system's gimbal which is attached to the sensor. It will measure these post-sensor dynamics during motion of the pre-sensor system as an impedance effect. These post-sensor dynamics can be thought of as the known time-invariant impedance of the interaction dynamics, and is preferably solely inertial in nature. These post-sensor dynamics do not include the user's dynamics. We therefore deem the user's impedance to be the unknown impedance Z_h. Instead of the force sensor, the post-sensor dynamics interact with a human limb or another object in the environment. The consequential interaction force is measured by the force sensor. The admittance controller will, due to these forces, attempt to respond like the virtual dynamics.

This can be demonstrated more technically in Figure D.13, which demonstrates a baseline model as a robotic system similar to D.12 expanding properties of the electomechincal example. The robotic in Figure D.13 is constructed with a rigid-body mass with added dissipation. External forces directed from a human are denoted as F_{ext} and provide human impedance (dotted grey area in the figure).

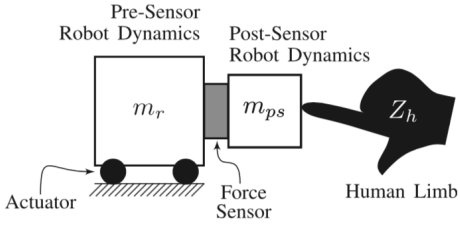


Figure D.12: Simplified electromechanical system diagram of a generic admittance controlled device. Extracted from [230]

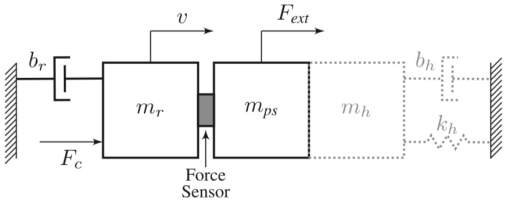


Figure D.13: Schematic view of a rigid robot. Extracted from [230]

The equation of motion of the system in Figure 5, omitting the human impedance, absorbing any external force (either from human impedance or extraneous force) into $F_ext(t)$ is given by:

$$(m_r+m_ps)\dot{v}(t)+b_rv(t)=F_{ext}(t)+F_c(t)+k_rF_{dst}(t) \tag{D.26}$$

with m_r the pre-sensor robot inertia and m_ps the post-sensor robot inertia, $v(t)$ the real robot velocity, b_r the viscous effects in the drive train, k_r the transmission ratio of the drive

train, $F_{ext}(t)$ the external force applied by the user (directly felt by the robot actuators), $F_c(t)$the force applied by the controller through actuators and transmission, and $F_{dst}(t)$ disturbance forces acting on the robot on the actuator side. The above equation is rewritten as:

$$(m_r s+b_r)v=F_{ext}-m_p svs+F_c+k_r F_{dst} \tag{D.27}$$

The controller equations for this baseline model for virtual dynamics of inertial form (virtual inertia m_v) are given by:

$$Y_v=\frac{1}{m_v s} \tag{D.28}$$

$$v_d=k_r Y_v(F_{ext}-m_{ps}vs) \tag{D.29}$$

$$F_c=k_r\frac{k_p s+k_i}{s}(v_d-k_r v) \tag{D.30}$$

with k_p and k_i the proportional and integral controller gains, respectively. Equation (4) gives the transfer function of the virtual dynamics. Equation (5) shows that the reference velocity is calculated from the measured interaction force, namely external force $F_{ext}$and the post-sensor inertial effects $-m_{ps}vs$. Equation (6) shows a typical PI velocity controller that generates a controller force based on the velocity error $e_v=v_d-k_r v$.

Keemink et al [230] in 2018 provides a series of guidelines and motivations when designing admittance control systems. The associated table can be seen in Table D.1.

Admittance control guidelines	
Guideline	Motivation
Use feed-forward control	Effectively lowers the robot inertia to be reduced by the admittance controller
Avoid force filtering	Introduces excessive phase-lag onto marginally passive virtual inertia model
Compensate post-sensor inertia	Reduces the apparent inertia, but significantly reduces coupled stability margins
Use some virtual damping	Allows for better low-frequency tracking of admittance
Modify the velocity reference	Non-physical phase-lead can give better tracking of pure inertial model and increases coupled stability margins
Increase velocity loop bandwidth	Pushes the excessive phase lag to higher frequencies, which requires higher environment stiffness to destabilise the coupled system
Optimise for robot stiffness	Internal resonant modes introduce phase lag between force sensor measurement and velocity measurement

Table D.1: Admittance control guidelines as stated by [230] and associated motivations

These guidelines along with the haptic resolution (3000 times higher than the haptic resolution of a Phantom desktop haptic device) and the fore-mentioned large workspace provides a suitable platform for the HapticMASTER to be used in the research.

It is crucial to have a large workspace when working with upper limb rehabilitation due to the range of movement expected of participants during the sessions. Movements can be scaled but in order to achieve believable movements made by participants a haptic robot utilising admittance control is required. Also having a far greater haptic resolution is beneficial in order to provide appropriate force feedback to create the illusion to the participant that their arm is colliding with solid objects such as the table etc and not just holding light objects such as blocks or light shopping.

D.1.6 Haptic Effects

Mathematically the basic concepts of the GOD algorithm are simple and therefore fast. Lagrange multipliers are used given active constrains to calculate the new GOD object position. In a 3 dimensional space were x,y&z denote the co-ordinates for the GOD object and x_p,y_p&z_p denote the co-ordinates for the HIP; then the energy in a virtual spring exhibiting unity stiffness can be calculated as:

$$Q=\frac{1}{2}(x-x_p)^2+\frac{1}{2}(y-y_p)^2+\frac{1}{2}(z-z_p)^2 \tag{D.31}$$

Constraints are added in the form of planes in first order in terms of x,y&z as:

$$A_n x+B_n y+C_n z-D_n=0 \tag{D.32}$$

Now the new location of the GOD object is derived by minimising L, setting 6 partial derivatives $(x,y,z,l_1,l_2\&l_3)$ to 0 due to these constraints being of first order and Q in the first equation being of second order. Resulting in:

$$\begin{aligned} L=&\frac{1}{2}(x-x_p)^2+\frac{1}{2}(y-y_p)^2+\frac{1}{2}(z-z_p)^2 \\ &+l_1(A_1x+B_1y+C_1z-D_1) \\ &+l_2(A_2x+B_2y+C_2z-D_2) \\ &+l_3(A_3x+B_3y+C_3z-D_3) \end{aligned} \tag{D.33}$$

Coefficient values which are seen in the equation above can be substituted in a symmetric matrix below:

$$\begin{bmatrix} 1 & 0 & 0 & A_1 & A_2 & A_3 \\ 0 & 1 & 0 & B_1 & B_2 & B_3 \\ 0 & 0 & 1 & C_1 & C_2 & C_3 \\ A_1 & B_1 & C_1 & 0 & 0 & 0 \\ A_2 & B_2 & C_2 & 0 & 0 & 0 \\ A_3 & B_3 & C_3 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} x \\ y \\ z \\ l_1 \\ l_2 \\ l_3 \end{bmatrix} = \begin{bmatrix} x_p \\ y_p \\ z_p \\ D_1 \\ D_2 \\ D_3 \end{bmatrix} \tag{D.34}$$

D.1.6.1 Friction Cone Algorithm

Friction can be defined as the output force resisting the movement of material elements moving against each other. Dry friction also be divided into two main subsections; static and kinetic friction. Dry friction can be simply modelled as Coulomb friction; where F_f denotes the net force of friction exerted by each surface on the other, μ denoting the coefficient of friction & F_n denoting the normal force exerted by each surface on the other. Giving:

$$F_f \leq \mu F_n \tag{D.35}$$

The important element in Coulomb friction is the coefficient of friction μ which can

take a set of numerical values for different material for both static friction μ_s and kinetic friction μ_k. A sample table of these values can be seen

		Coefficient of Friction			
		Dry		Greasy	
Mat. 1	Mat 2.	Static	Sliding	Static	Sliding
Brake Material	Cast Iron (Wet)	0.2			
Brass	Cast Iron		0.3		
Brick	Wood	0.6			
Bronze	Cast Iron		0.22		
Bronze	Steel			0.16	
Cadmium	Cadmium	0.5		0.05	
Cadmium	Mild Steel		0.46		
Cast Iron	Cast Iron	1.1	0.15		0.07
Cast Iron	Oak		0.49		0.075
Chromium	Chromium	0.41		0.34	
Copper	Cast Iron	1.05	0.29		
Copper	Copper	1.0		0.08	
Copper	Mild Steel	0.53	0.36		0.18
Copper-Lead Alloy	Steel	0.22			
Diamond	Diamond	0.1		0.05-0.1	
Diamond	Metal	0.1-0.15		0.1	
Glass	Glass	0.9-1.0	0.4	0.1-0.6	0.09-0.12
Glass	Metal	0.5-0.7		0.2-0.3	
Glass	Nickel	0.78	0.56		

Figure D.14: Example table showing a sample of coefficient values both μ_s and μ_k

What this simplified look at friction provides in the context of the friction cone algorithm is that adding various material effects can be achieved by a series of coefficients.

Friction can be modelled as Lischinsky et al describes as "a discontinuous static map between velocity and friction torque which depends on the velocity's sign" [231] and can be visually depicted in figure D.15. However friction also has dynamic properties such as, stick-slip motion, presliding displacement and frictional lag.

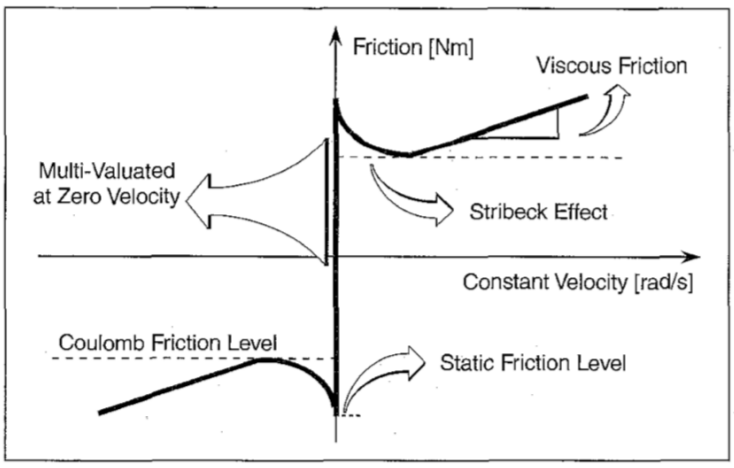


Figure D.15: Friction velocity description. Extracted from [231]

As stated above the friction cone algorithm is an amendment to Zilles et al [209] GOD object algorithm, by the addition of a cone at the location of the HIP which is rotated facing the direction of the surface/mesh. This cone is visually shown in with the friction angle being calculated as: (were μ defined as previously, the coefficient of friction)

$$\tan\theta = \frac{MaxFrictionForce}{Normal/ReactionForce} = \mu \tag{D.36}$$

The intersection of this cone with a planar surface on an mesh/object will provide a definition of the friction circle since the surface is normal to the cone.

With the traditional god object algorithm both the HIP and GOD objects are collocated. The friction cone algorithm takes the approach that the GOD object should only be moved if the GOD object is located outside the previously defined circle projected by the friction cone. This can be visually seen in figures D.16 and D.17.

The depth of penetration derived from the HIP in relation to the surface of the mesh/object combined with the surface and the coefficient of friction value to calculate the size of the circle resulting in the projected friction cone. This simple equation is defined as with ρ_{fp} denoted as the radius of the friction circle and HIP_d denoted as the depth of the HIP:

$$\rho_{fp} = \mu \dot{HIP}_d \tag{D.37}$$

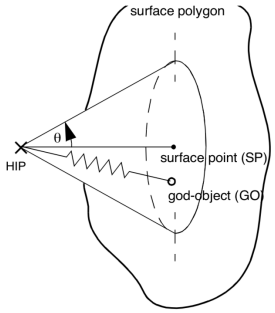


Figure D.16: Visual example of the friction cone algorithm with the GOD object inside the friction cone.Extracted from [210]

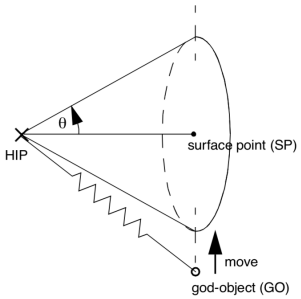


Figure D.17: Visual example of the friction cone algorithm with the GOD object outside the friction cone.Extracted from [210]

The last step is is to calculate the the forces that are to be sent to the haptic robot servos derived from the 3D position of the GOD object and HIP. A direction vector from the HIP to the GOD object is used to implement the correct forces to be sent to the haptic robot once a collision has occurred.

In addition to this parameter forces acting on a virtual object/mesh are calculated as a result again using a direction vector from the GOD object to the HIP. These forces and parameters are stored as vectors in 3D format.

The core element of the friction cone algorithm is the HIP, in that the HIP determines were the cone is located which poses issues when the algorithm is used in its intend purpose which is multi-point environments involving multiple HIPs. Object manipulation with more than one HIP requires multiple forces acting on the object/mesh. This is solved by summing all the forces which are stored as vectors providing a final residual force for that given object/mesh.

Residual torque is generated due to these resulting force moments at the point of the virtual object's centre of gravity. As per previous forces, this torque is stored in a vector which can be used to implement how the virtual object reacts physically to the final applied force. This also applies to other physics based variables which can be derived from the virtual object such as the centre of mass and moments of inertia and allows correct calculation of gravity and rotational forces. Gravity is simply a vector force with just the third variable set in the z axis and rotational forces are calculated via moments around the virtual object's centre of mass.

D.2 Swing and Twist IK

What was needed was a simplified, fast and reliable technique which had proven results and allowed not just arm kinematics but body posture too to allow leaning when using the system. A brief review of existing frameworks lead to the discovery and implementation of Kallmann's technique [232] based on Swing-and-Twist arm inverse kinematics. The benefits of using this approach is that the parameterisation (due to swing-and-twist rotation decomposition or exponential map) of the joints based on swing-twist naturally controls collision avoidance and joint coupling and gimbal lock. Also by including whole body posture allows the technique to be adapted to our needs more efficiently. As such Kallmann's technique is one of the fastest whole body IK solvers with collision avoidance. A brief over view on how the technique works is presented below with a more indepth formalisation afterwards.

In essence the swing and twist technique takes a given position and orientation (a vector and quaternion respectively) and works out the swivel angle which is how much the mid joint (elbow) has rotated around the end(wrist)-base(shoulder) axis. With the swivel angle

calculated the mid flexion, base swing, base twist, mid twist and end swing can be calculated to produce the required joint values. Which before being assigned to the joints are checked against the joint limits (a predetermined spherical ellipse), which provides not just the limits but the collision avoidance too.

Below shows how the algorithm works for the right arm.

Given a point $\boldsymbol{e} \in \mathbb{R}^3$ and a quaternion $\boldsymbol{q}_e \in \mathbb{S}^3$ (chosen position/orientation of the end joint, wrist bone) work out the swivel angle ϕ. The computed values are put into an array $(v_0,...,v_6)$ corresponding to the 7 DOF values d_1 refers to the length of the upper arm and d_2 the length of the lower arm.

D.2.1 Swivel Angle

To work out ϕ, two-unit vectors $\hat{u}$ and $\hat{v}$ are used to create a local coordinate system resulting in a plane containing the orbit circle for the elbow. $\hat{u}$ defined as the projection of the $-\hat{y}$ axis onto the orbit circle plane, $\hat{v}$ orthogonal to $\hat{u}$. Also defined is $\hat{n}$ which is the normalised vector from the base joint to the end joint.

$$\hat{u} = \frac{-y + (y \cdot n)n}{\| -y + (y \cdot n)n \|} \tag{D.38}$$

$$v = u \cdot n \tag{D.39}$$

$$\hat{n} = \frac{e}{\|e\|} \tag{D.40}$$

Once these unit vectors have been defined the final elements of the orbital circle can be defined, the centre c and radius r which can be derived by:

$$c = \hat{n} d_1 \cos\alpha \tag{D.41}$$

$$r = d_1 \sin\alpha \tag{D.42}$$

Where $\cos\alpha$ and $\sin\alpha$ defined as:

$$\cos\alpha = \frac{d_1^2 + d_2^2 - \|e\|}{-2d_1\|e\|} \tag{D.43}$$

$$\sin\alpha = \frac{d_2 \sin(\pi - v_3)}{\|e\|} \tag{D.44}$$

Once the complete orbital circle has been completed the mid joint (elbow) position $m$can be obtained with:

$$m = c + r(\hat{u}\cos\phi + \hat{v}\sin\phi) \tag{D.45}$$

D.2.2 Mid Flexion

The mid flexion $v_3$forms the triangle using d_1,d_2 and $\|e\|$ as the sides. With it's value being derived by, with the solution with the minus sign being assigned to v_3:

$$v_3 = \pi \pm \arccos\left(\frac{d_1^2 + d_2^2 - \|e\|}{2d_1 d_2}\right) \tag{D.46}$$

D.2.3 Base Swing

The base swing rotation is computed by the rotation needed to bring the upper limb into the zero position to the mid position m. The paper's coordinates are different to the coordinates used by Unreal Engine. Therefore the rest of the equations use Unreal Engine's coordinates rather than the paper's (the paper's z axis is Unreal Engine's x axis).

The axis of rotation is for the base swing is $\hat{x} \cdot m$and the rotation angle is the angle between $\hat{x}$ and m Due to the fact that the axis of rotation is always in the zy -plane of the base local frame the 2D axis angle representation of the swing rotation can be derived as:

$$\begin{pmatrix} v_0 \\ v_1 \end{pmatrix} = \begin{pmatrix} S_z \\ S_y \end{pmatrix}, s = \frac{\hat{z} \cdot m}{\|\hat{z} \cdot m\|} \arccos\frac{\hat{z} \cdot m}{d_1} \tag{D.47}$$

Where s_z and $s_y$are the z and y elements of s.

D.2.4 Base Twist

In order to find the base twist a quaternion $q(a)$is used with $\|a\|$ as the rotation angle:

$$q(a) = \left(\cos\frac{\|a\|}{2}, \frac{a}{\|a\|}\sin\frac{\|a\|}{2}\right) \tag{D.48}$$

Once this rotation is applied to the base joint v_2, will make the joint link rotate in order for the end joint to reach e. If f is the end joint position when v_3 is applied to the linkage

in the zero position f becomes:

$$f = q_{(0,v3,0)} \begin{pmatrix} d_2 \\ 0 \\ 0 \end{pmatrix} q_(0,v3,0)^{-}1 + \begin{pmatrix} d_1 \\ 0 \\ 0 \end{pmatrix} \tag{D.49}$$

With g being the goal end position e rotated by the inverse of the base swing rotation:

$$g = q^{-1}_{(0,v1,v0)} e q_{(0,v1,v0)} \tag{D.50}$$

In order to determine v_2 a rotation matrix is used around $\hat{x}$ that brings f to coincide with g is used:

$$\begin{pmatrix} \cos v_2 & -\sin v_2 & 0 \\ \sin v_2 & \cos v_2 & 0 \\ 0 & 0 & 1 \end{pmatrix} f = g \tag{D.51}$$

To solve the equality above the following is used to finally compute v_2:

$$\arctan v_2 = \frac{f_z g_y - f_y g_z}{f_z g_x + f_y g_y} \tag{D.52}$$

D.2.5 Mid Twist and End Swing

The mid twist and end swing rotations despite being applied to two different joints the combination of the two is the same as a single 3 DOF rotation q. Which is first calculated then decomposed into the separate mid twist and end swing elements.

Assembling all the computed rotations calculated above in order the following identity can be deduced:

$$q_{(0,v1,v0)} q_{(v2,0,0)} q_{(0,v3,0)} q = qe \tag{D.53}$$

With q being obtained via:

$$q = (q_{(0,v1,v0)} q_{(v2,0,0)} q_{(0,v3,0)})^{-}1 qe \tag{D.54}$$

Once q has been obtained in the correct quaternion format, v_4 can be extracted (mid twist) around the x axis and v_5,v_6(as the 2D axis angle of the end joint swing).

If q_x and q_w are both zero the orientation is at the singularity of the swing element. How-

ever due to the settings of the joint limits this should never happen due to the limits ensuring that any rotations stay away from the singularity ($-\hat{x}$ direction from the local frame).

As a result the identity holds given:

$$q_{(v4,0,0)}q_{(0,v6,v5)} = q \tag{D.55}$$

Extracting v_4 from the above identity can be achieved by:

$$\begin{pmatrix} v_5 \\ v_6 \end{pmatrix} = \frac{2\beta}{\sin\beta} \begin{pmatrix} \sin\frac{v_4}{2} & -\cos\frac{v_4}{2} \\ -\sin\frac{v_4}{2} & \cos\frac{v_4}{2} \end{pmatrix} \begin{pmatrix} q_z \\ q_y \end{pmatrix} \tag{D.56}$$

Where β is defined as:

$$\beta = \text{atan2}\left(\sqrt{q_x^2+q_y^2}, \sqrt{q_z^2+q_w^2}\right) \tag{D.57}$$

All DOFs have been finally computed $(v_0,...,v_6)$

D.2.6 Joint limits

In order to ensure correct swing limits (for v_0,v_1 the base swing & v_5,v_6 for the end swing) spherical ellipses are used in the zy local plane. Swing rotations in a 2D rotation $(s = (s_z,s_y))$ are considered to be valid related to its jointĂŹs limiting ellipse with semi axes lengths r_z,r_y if the below inequality holds:

$$\left(\frac{s_z}{r_z}\right)^2 + \left(\frac{s_y}{r_y}\right)^2 \leq 1 \tag{D.58}$$

With regards to and minimum/maximum limits for the other values v_2,v_3&v_5 they are considered correct if they meet specific Euler angle limits.

Appendix E

Additional Supporting Data

E.1 Proprioceptive Drift

Figure E.1 shows average measurements within several conditions; Difference in distance (between post and pre)in the x axis only, difference in distance (between post and pre)in the y axis only, pre distance in the x axis only, post distance in the x axis only, pre distance in the y axis only and post distance in the x axis only.

Unlike Figure 8.10, Figure E.1 do show more variation in values although mainly in the pre and post difference average in the y axis only. The data does suggest an improvement in alignment (x axis) within group VH over group V but also the opposite in telescoping (y axis), with group V seeing an improvement in distance over group VH. Due to the fact that the virtual hand position is know, a more in-depth analysis should be carried out to see if the virtual hand position is aligned and telescoped with the drift measurements between the groups.

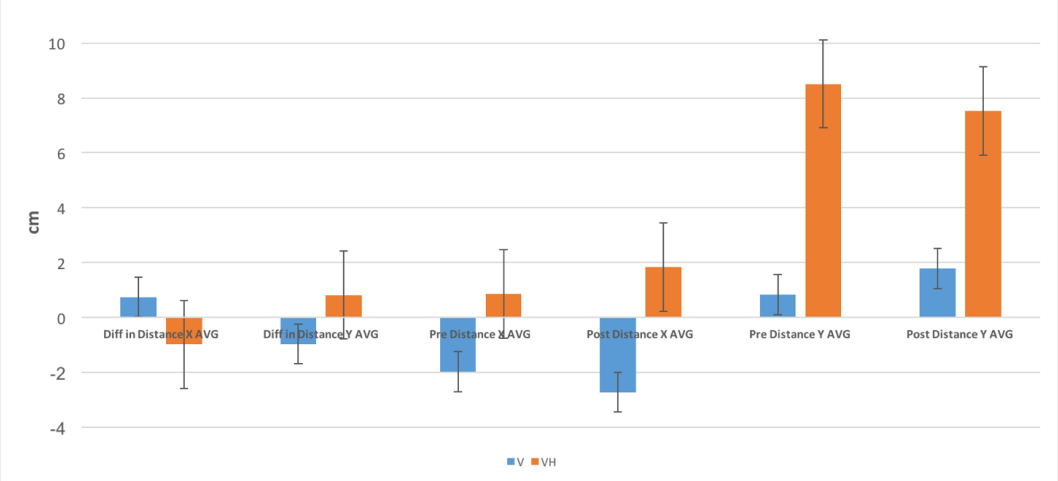


Figure E.1: Various average proprioceptive drift measures between groups. 95% CI and STD.

A single factor Anova was carried out for the mean distance in the x axis with the full results found in Table E.1. With a p-value of 0.1, no statical significance can be drawn from the mean distance in the x axis.

Anova: Single Factor **Distance X AVG**

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Group V	9	6.76	0.751111111	8.437611111
Group VH	9	-8.816666667	-0.97962963	5.148109568

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	13.4795858	1	13.4795858	1.984375525	0.17806673	4.493998478
Within Groups	108.6857654	16	6.79286034			
Total	122.1653512	17				

Table E.1: Single Factor Anova results between the two groups over 9 sessions mean distance in the x axis.

A single factor Anova was carried out for the mean distance in the y axis with the full results found in Table E.2. With a p-value of 0.3, no statical significance can be drawn from the mean distance in the y axis.

Anova: Single Factor **Distance Y AVG**

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Group V	9	-8.62	0.957777778	14.25544444
Group VH	9	7.416666667	0.824074074	16.82549383

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	14.2874821	1	14.2874821	0.919372638	0.351905827	4.493998478
Within Groups	248.6475062	16	15.54046914			
Total	262.9349883	17				

Table E.2: Single Factor Anova results between the two groups over 9 sessions mean distance in the y axis.

E.2 Phantom Hand

One factor to take into consideration is the element of increased Phantom Hand sensation/-control. This is a result of embodiment data being inconclusive in terms of showing a link between pain and embodiment or at least not significant.

As shown in Figure E.2. During the sessions and baseline/follow up sessions participants were asked about the Phantom hand and how much control they had in their hand or the general sensation/representation. Going over the written sheets, if there was a noted

improvement over any aspect of the Phantom hand. Of the twelve participants, ten participants stated that they experienced an improvement.

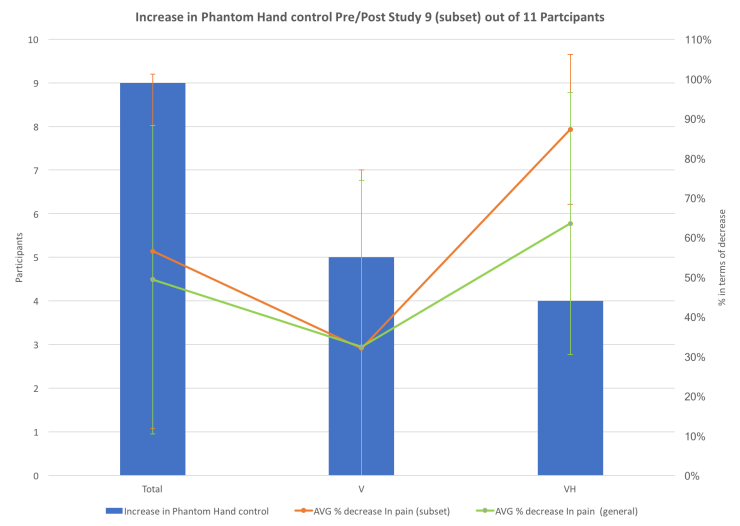


Figure E.2: Subset results from participants who experienced an increase in Phantom Hand sensation or control. 95% CI and STD.

Starting with the total number of participants who experienced an improvement regardless of the group, nine participants experienced on average 57% (STD 39%) pain decrease compared to the overall average pain decrease 39% (STD 39%) pain decrease giving a difference of 7%.

Interestingly in this subset of participants within the control group all five stated they experienced some control or sensation of their Phantom hand during the clinical study, with the average decrease in pain for the subset and general being 32% (STD 42%) regardless of the participants improved Phantom hand.

What makes this fact interesting is comparing this to the experimental group who received haptic feedback. Out of the six participants in total within that group, four (66%) stated that they experienced an increase in control/sensation. However unlike the control group the average pain decrease within this subset was 87% (STD 19%) which when compared to the general decrease in pain within the experimental group at 64% (33%) yields a 24% difference, marking a significant difference between those who experienced improved control or sensation of their Phantom hand compared to those who did not.

Whilst the embodiment questionnaires and drift measures do not suggest a strong effect between groups using the increase in control/sensation does show significant differences.

This subset of data can be further broken down into additional subsets based on previous

data calculating the effectiveness of the intervention (50% > effectiveness and < 50% effectiveness), with the data representing the > 50% effectiveness shown in Figure E.3 and figure E.4 representing data from the subset of those who achieved < 50% effectiveness.

Figure E.3 shows the further subset of those participants who experienced greater control and sensation with their Phantom hand who experienced a 50% or greater decrease of pain during the clinical study. Five participants of the improved Phantom hand control/sensations out of eleven total are included within this subset: For one from the control group (out of five) and four (out of six) from the experimental group, giving a total of 5 within this subset, the average decrease in pain was 90% (STD 17%) compared to the general overall decrease of 49% (39%) resulting in a 40% difference. One participant from the control group experienced a 100% decrease compared to 32% (STD 42%) giving a 68% difference.

Four out of six of the participants from the experimental group who experienced improved Phantom hand control/sensations are also included within this subgroup with the average decrease in pain being 87% (STD 19%) compared to the whole group average decrease of 64% (STD 33%) giving a difference of 24%.

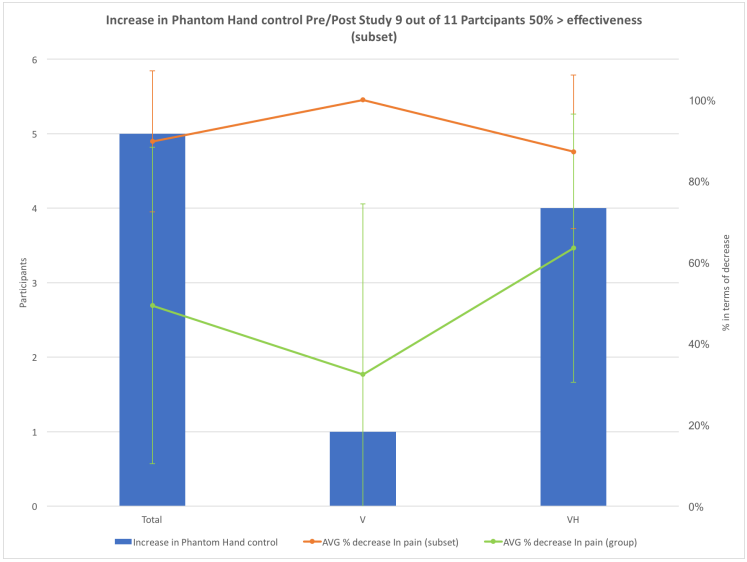


Figure E.3: Subset results from participants who experienced an increase in Phantom Hand sensation or control, broken down into a further subset of those greater than 50%. 95% CI and STD.

Taking into consideration those who experienced an increase in Phantom hand control/sensation that whoever experienced less than 50% decrease in pain shows a total of four participants, with all four being in the control group as shown in Figure E.4.

The average decrease in pain for this whole subset was 15% (STD 28%) compared to the

average pain reduction for all participants at 49% (STD 38%) providing a difference of 34%. This 15% decrease is the same value for the 4 control group participants who are in this subgroup, however the general decrease in the control group is 32% (STD 42%) which brings the difference closer between the two to 17%, half of the total decrease of all the participants.

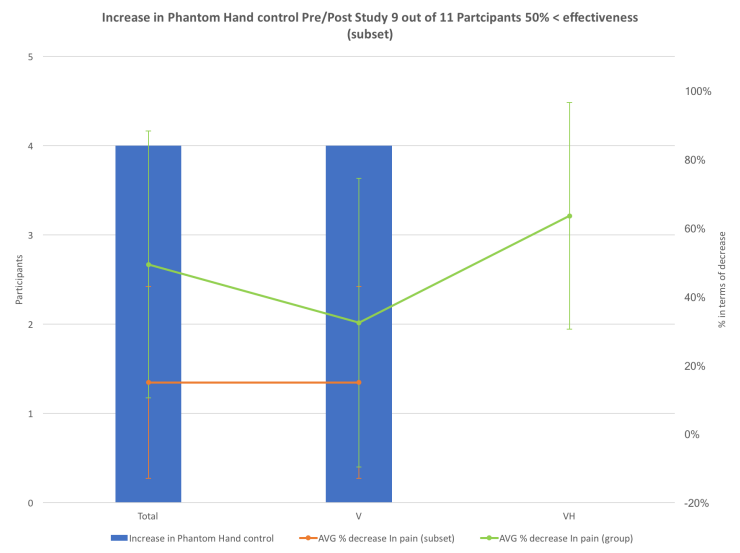


Figure E.4: Subset results from participants who experienced an increase in Phantom Hand sensation or control. Broken down into a further subset of those less than 50%. 95% CI and STD

These results provide a clearer picture of not just in session embodiment which yielded variable results but also a clear definition that the experimental group not only experienced better levels of decrease but also in terms of improved Phantom hand control and sensation which could be argued falls in line with both levels of embodiment and agency.

This is in line with current research which has switched to the former hand area as opposed to general embodiment. The improved control/sensation also takes into consideration both embodiment and agency which is also a positive when used as a measure combined with questionnaire/drift.

The issue of measuring long term embodiment and agency could be potentially addressed with this measure of Phantom hand control/sensation, although what is lacking in this study is a numerical value pre and post intervention as well as inter sessions. However accurately determining the Phantom hand position and configuration could prove difficult to replicate.

The issue remains in study participants and amputees in general who's Phantom hand via traumatic amputation can be considered "disfigured" e.g like putting individual fingers into a bag and emptying the contents out on the floor. Which was a comment by one of

the participants when describing the configuration of their Phantom hand. This does lead into questions such as the quality of the initial Phantom hand and whether or not this has an effect of the effectiveness the participant finds therapy such as AMPSIM or any visual surrogate based therapy.

Appendix F

Prototype Haptic architecture

Initially a virtual reality creation software was used called Vizard. Similar although not as widely used as Unreal Engine; Vizard is programmed in Python and allows the use of specific hardware out the box and custom hardware via use of the Vizard Software Development Kit (SDK). It was this SDK that was used to create a .dll file readable by Vizard in Python that allowed communication between the software (Vizard) and hardware (HapticMASTER via Haptic Server). In order for this initial prototype to work the the following aspects had to be included.

1. The visual layer and haptic layer were separate. With the haptic objects such as cubes being created on the haptic renderer when the exercise was initialised.
2. On visual update the cube's position and orientation was sent back and forth from Vizard to the haptic renderer on the HapticMASTER. Thus creating a two way communication to visually and haptically render the objects in real time.
3. This also included sending the specific haptic properties such as friction coefficients and stiffness.
4. Appropriate scalars were added on both ends due to different co-ordinate origins. 0.22 meters subtracted to the HapticMASTER Z (vertical) axis due when sending object data updates to the haptic renderer so to correctly place the object at table level, and the opposite (add 0.22 meters) when sending the data back to Vizard.
5. Data from the HapticMASTER's force sensors including position and gimbal orientation were also polled in real time and sent to Vizard, again with scalars applied to update the position of the end effector etc visually.

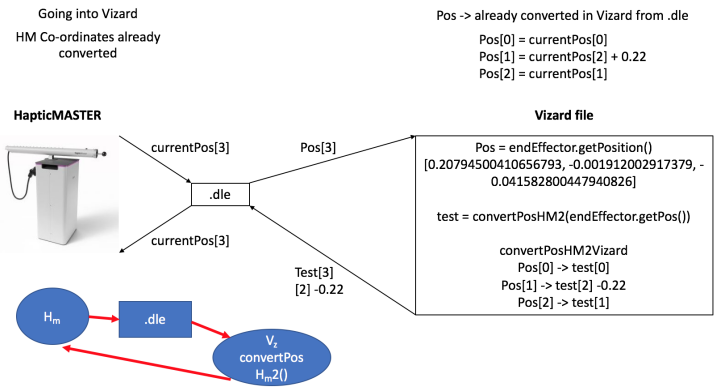


Figure F.1: Schematic representation of the prototype haptic architecture used between Vizard and the HapticMaster. Going out of Vizard co-ordinates are converted into 1:1 H_m co-ordinates via the $convertPosHM_2()$ method inside Vizard which is then sent to the HapticMaster. Along with a state diagram on the bottom left of the figure.

F.1 Ethics Related Documents

F.1.1 Participant Information Sheet

Participant Information Sheet for Adults

Version 2.0

12.05.2015

Project Title: A pilot study to compare Virtual Reality (VR) versus VR plus haptic feedback as a medical intervention to decrease upper limb phantom pain responses in amputees

Chief Investigator: Dr Rui Loureiro
Principal Investigator: Dr Imad Sedki

Sponsor: Middlesex University (in partnership with UCL) funded through the Ministry of Defence (Dstl National PhD Scheme, contract No: DSTLX-1000064225

We would like to invite you to take part in a research study. Before deciding if you will give permission to take part in this study, you need to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Although the study is funded by the Ministry of Defence only NHS patients will be participating in the study.

Why have I been invited?

You are being asked to take part in this study because you have sustained an amputation and you now experience pain in your absent limb (phantom pain).

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to read and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

Why is this study being done?

A large percentage of amputees (50-80%) experience feelings and sensations in their amputated limbs, with varying degrees of severity. Of these, phantom limb pain (i.e. pain appearing to come from where an amputated limb used to be) can be one of the most distressing and debilitating.

The origins of phantom limb pain are not well understood and it is therefore very difficult to treat. It has been suggested that phantom limb pain arises as a result of the absence of feedback from the missing limb, to the otherwise intact motor control regions of the brain. When we want to move, signals are sent from our brain to the part of our body we want to move. The brain receives feedback about the movement primarily through our sense of touch and vision, but also from our other senses. Following amputation, the brain will continue to send instructions to the missing limb,

some conscious and some unconscious, but will not receive any feedback, and it is thought this results in the sensation of pain.

What we want to investigate in this research is whether it is possible, through the use of modern technology, to reduce phantom limb pain through a series of computer controlled tasks.

What is proposed in this research is to employ state of the art virtual reality (VR) glasses in conjunction with a haptic robot (a mechanical device that follows the arm's movements) that will create a much more realistic illusion for the wearer. The haptic robot may also provide force feedback (haptic feedback) when the user manipulates objects. The volunteer will be asked to perform a number of tests on a number of occasions, and any perceived changes in phantom limb pain will be evaluated.

What will I have to do?

You will be asked to take part in a series of tasks (e.g. moving virtual objects) while using the VR equipment and with your residual limb connected to a haptic robot, which is a mechanical device that follows your arm's movements and might also provide haptic feedback (e.g. feeling of forces) when the user manipulates virtual objects (see Figure 1 and Figure 2). This will involve a total of nine hours of intervention over nine sessions (one hour each) during a three-week period (three each week). During each session, 30 minutes will be taken up performing games (tasks) using the haptic robot system (see Figure 1 and Figure 2), 10 minutes at the start and at the end of the session will be allocated to setting up and taking off the sensors, performing some measurements and completing questionnaires (e.g. embodiment and pain questionnaires) assisted by the research team. During each session we will record a variety information such as the movements you will make (both from intact and residual limb), muscle activity using EMG electrodes placed on the surface of the skin and other physiological parameters such as respiration, skin temperature and conductance. In addition, you will be allowed to take up to 10 minutes break from the VR equipment and haptic robot system during each session. We will need to perform one further assessment three weeks after completing the study to assess whether there have been any longer term effects as a result of taking part in the sessions. You will be asked to keep a pain diary for the length of the study until the final follow up.

Volunteers will be put into groups, with each group being asked to complete different tasks. The results will then be compared to see if certain tasks appear to be more effective in reducing phantom limb pain than others.

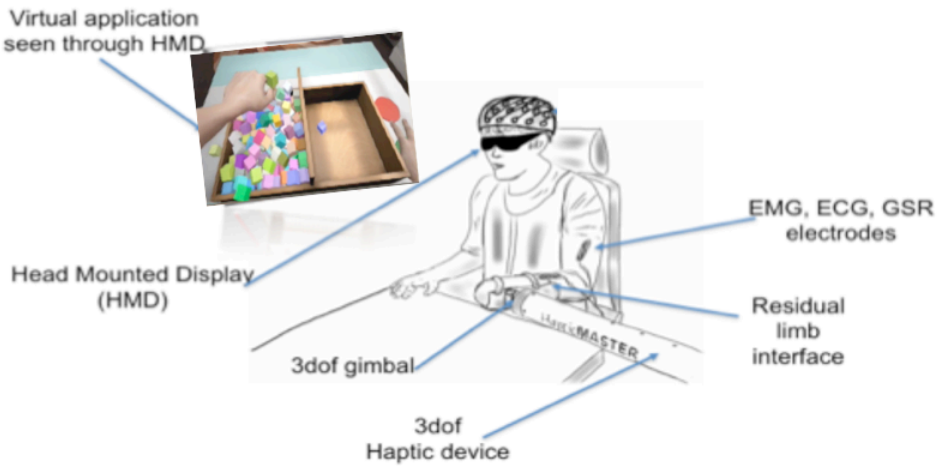


Figure 1: Conceptual illustration of the VR equipment and haptic robot system.

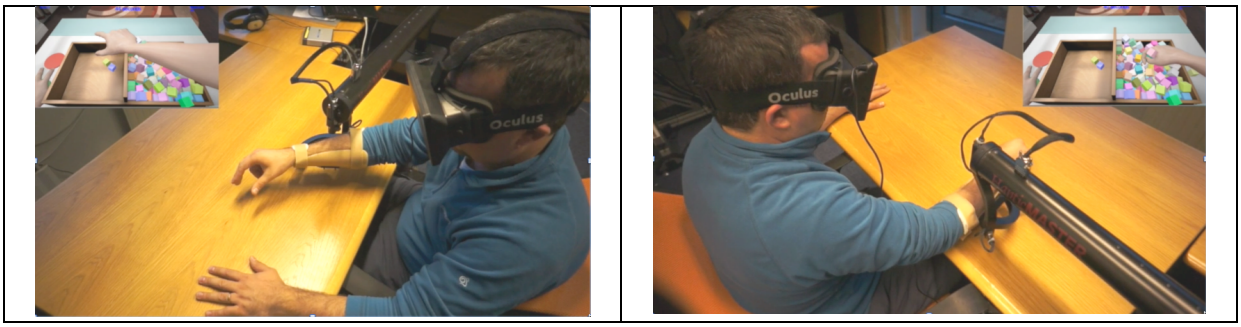


Figure 2: Able-bodied individual using the VR equipment and haptic robot system while wearing the VR glasses. Top left/right image is the virtual task (application) seen through the VR glasses (also known as Head Mounted Display).

What are the possible disadvantages and risks of taking part?

There are no identifiable risks to participants. The VR equipment and haptic robot system should not present any inconvenience or distress for the user.

In the unlikely event that you feel increased discomfort or pain, you will be advised not continue to participate in the study.

What are the side effects of any treatment received when taking part?

There is a small chance that the treatment might cause you temporary increased pain, or temporary nausea or other distress. Experts will be on hand to assess you, should it be deemed too uncomfortable then you will be withdrawn.

What are the possible benefits of taking part?

We cannot promise the study will help you personally but the information we get might help people with phantom limb pain in the future. Your contribution will help us towards establishing a more solid scientific framework for advancing the knowledge of using the haptic robot system in the treatment of injured or missing limbs.

What happens when the research study stops?

The results of the study will be published in scientific journals and will be part of a PhD thesis at Middlesex University. The results obtained with this study will help us towards establishing a more solid scientific framework for advancing the knowledge of using the haptic robot system in the treatment of phantom limb pain.

Are there any expenses and payments which I will get?

An Amazon voucher (with a value of £100) will be given to you at the end of the study for the inconvenience of taking part in the trial. We will also provide contributions of up to £50 per session for reimbursement of travel expenses.

Part 2

What will happen if I don't want to carry on with the study?

Participation is entirely voluntary and you have the right to withdraw from the project at any time simply by notifying the investigators without detriment to any care or services you may be receiving or may receive in the future. We just ask that you keep in contact with us to let us know your progress. Information collected may still be used for research unless you specifically instruct otherwise.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [contact number]. If you remain unhappy and wish to complain formally, you can do so via the normal National Health Service complaints mechanisms will still be available to you.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Middlesex University and the Ministry of Defence but you may have to pay your legal costs.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will be notified of your participation in this trial, if you agree to let us do so.

What will happen to the results of the research study?

The results of the study will be published in scientific conferences/ journals. All the data presented will be anonymised and you will not be identified in any report/ publication. Up on request a summary of the results will be made available to participants.

Who is organising and funding the research?

This investigation is part of research at Middlesex University in collaboration with University College London. The research is funded by the Ministry of Defence through the Defence Science and Technology Laboratories National PhD Scheme, contract No: DSTLX-1000064225).

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by _____Research Ethics Committee.

Who do I contact for general information about research?

You can contact the R&D office via research@rnoh.nhs.uk or 02089095529

Who do I contact for specific information about this research project?

Principal Investigator: Dr Imad Sedki, Consultant in Rehabilitation Medicine, The Prosthetic Amputee Rehabilitation Centre, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, HA7 4LP. 0208 909 5505

Chief Investigator: Dr. Rui C.V. Loureiro, Head of Centre, Aspire Centre for Rehabilitation Engineering and Assistive Technology, UCL Institute of Orthopaedics and Musculoskeletal Sciences, Division of Surgery & Interventional Science, University College London, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, HA7 4LP, UK. Phone: 0208 385 3049

Who should I approach if unhappy with the study?

Patient Advice and Liaison Service via pals@rnoh.nhs.uk or 020 8909 5439/5717

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F.1.2 Participant Consent Form

Royal National Orthopaedic Hospital
NHS Trust

RNOH Stanmore
Brockley Hill
Stanmore
Middlesex
HA7 4LP

Title of Project: A pilot study to compare Virtual Reality (VR) versus VR plus haptic feedback as a medical intervention to decrease upper limb phantom pain responses in amputees

Patient Identification Number for this trial:
Chief Investigator: Dr Rui Loureiro
Principal Investigator: Dr Imad Sedki

1. I confirm that I have read and understand the information sheet dated _____ Version_____ for the above study. ☐
2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from The Prosthetic and Amputee Rehabilitation Centre in Stanmore, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I agree to my GP being informed of my participation in this study. ☐
6. I agree to take part in the above research study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

When complete,
1 copy for patient:
1 copy for researcher site file
1 (original) in medical notes