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**Perceptual abnormalities in amputees:
Phantom pain, mirror-touch synaesthesia
and referred tactile sensations**

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the degree of Doctor of Philosophy

School of Psychology

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Declaration

I, Aviva Idit Goller, hereby declare that this thesis has not been submitted, in whole or in part, to this or any other university for the award of another degree. The work presented in this thesis is my own, and I confirm that where information has been derived from other sources this has been indicated in the text.

Aviva Idit Goller

September 2011

Preface

This thesis was written in the new European format. This means that each study or set of experiments was written as a paper that could be submitted to a scientific journal for publication. Preceding the papers is an overview that reviews the related literature and outlines the aims and findings of the current research. The structure of the overview reflects the order of the papers in the thesis. After generally introducing the research topic, each section of the overview discusses a different perceptual phenomenon, and then relates the literature to the thesis papers relevant to it. The general discussion at the end of the overview discusses how the findings from the various papers are connected to each other and the issues addressed in the thesis.

The research was funded by a three-year Graduate Teaching Assistantship from the University of Sussex, sponsored by the Life Sciences Ethics Committee at the University of Sussex and approved by the Brighton East Research Ethics Committee of the National Health Service.

Parts of this research have been presented at the European Workshop on Cognitive Neuroscience (Goller and Ward, 2009) and the Sense of Body Summer School (Goller and Ward, 2008).

The following publication has arisen from the thesis:

Goller, A. I., Richards, K., Novak, S., & Ward (2011). Mirror-touch synaesthesia in the phantom limbs of amputees. *Cortex*, DOI: 10.1016/j.cortex.2011.05.002.

The following publications are in preparation:

Goller, A.I. & Ward, J. (in prep). Changes in perception arising after amputation.

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Summary

It is often reported that after amputation people experience "a constant or inconstant... sensory ghost... faintly felt at time, but ready to be called up to [their] perception" (Mitchell, 1866). Perceptual abnormalities have been highlighted in amputees, such as sensations in the phantom when being stroked elsewhere (Ramachandran *et al.*, 1992) or when observing someone in pain (Giummarra and Bradshaw, 2008). This thesis explored the perceptual changes that occur following amputation whilst focusing on pain, vision and touch. A sample of over 100 amputees were recruited through the National Health Service. Despite finding no difference in phantom pain based on physical amputation details or non-painful perceptual phenomena, results from Paper 1 indicated that phantom pain may be more intense, with sensations occurring more frequently, in amputees whose pain was trigger-induced. The survey in Paper 2 identified a group of amputees who in losing a limb acquired mirror-touch synaesthesia. Higher levels of empathy found in mirror-touch amputees might mean that some people are predisposed to develop synaesthesia, but that it takes sensory loss to bring dormant cross-sensory interactions into consciousness. Although the mirror-system may reach supra-threshold levels in some amputees, the experiments in Paper 3 suggested a relatively intact mirror-system in amputees overall. Specifically, in a task of apparent biological motion, amputees showed a similar, although weaker, pattern of results to normal-bodied participants. The results of Paper 4 showed that tactile spatial acuity on the face was also largely not affected by amputation, as no difference was found between the sides ipsilateral and contralateral to the stump. In Paper 5 cross-modal cuing was used to investigate whether referred tactile sensations could prime a visually presented target in space occupied by the phantom limb. We conclude that perception is only moderately affected in most amputees, but that in some the sensory loss causes normally sub-threshold processing to enhance into conscious awareness.

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Overview

1. History, epidemiology and phenomenology: The phantom's story

JF was born with a palm-less left wrist that had what she referred to as "stubbins" in place of fingers. Her hand did not fully develop in utero and she was born with merely a couple of knuckle-like bumps atop her otherwise kinematically intact wrist. At the age of six her stubbins were surgically removed for cosmetic reasons, but the amputation left her with vivid ghostly sensations that the stubbins physically remained. Now, aged 63, JF still senses the presence of these illusory stubbins, and the feeling is of knuckles that are similar in size and quality to the ones she once had. Much to her surprise, when putting a glove on the end of her hand-less forearm, her stubbin sensations felt as though they had extended into full-length fingers! JF is one of the many amputees with remarkable phantom limb phenomena who have contributed to the current research – a thesis which aims to shed light on JF's perceptual experiences and those of other people with similar limb deficiencies. First we will look into the history of abnormal perceptual reports associated with amputation in the medical and psychological fields, followed by an outline of their epidemiology and a detailed description of perceptual phenomena experienced by amputees.

1. 1. History

Foremost, it is important to note that JF's illusory stubbins are "an illusion, not a delusion" (Ramachandran and Hirstein, 1998, p. 1604). Amputees are fully aware that their limbs have been severed and removed. The perceptual anomalies that follow amputation occur immediately and are mostly beyond volitional control (Melzack, 1992; Ramachandran and Hirstein, 1998). Such illusions of limb presence and sometimes pain have been described as early as the 16th century (Paré, 1551), and probably not before then simply because previously only few had survived amputation and were able to relay their experiences (Wade, 2003). Ambroise Paré (1510-1590) was a French military surgeon who made great advances in the development of amputation techniques. He was first to introduce mechanical prosthetic limbs to enable his patients' mobility and dexterity. In his autobiography, *The Apology and Treatise of Ambrose Paré*, he described how many of his patients would continue to grievously complain about pain in the body part which had been cut long after the limb had been removed and the wound healed (Paré, 1951). By the time of René Descartes (1596-1650) illusions of a maintained limb after amputation were common medical knowledge, and

Descartes (1637) used the phenomenon to argue in favour of a unified mind in contrast to the fragmented body, i.e. even when a part of the body is severed nothing is taken away from the mind.

Although the phenomenon had already been described in the 16th century, and from the time of Descartes multiple theoretical interpretations had been proposed, the defining term "phantom limb" was not introduced until late in the 19th century by Silas Weir Mitchell (1829-1914). Mitchell (1866) originally introduced the concept of phantom limb sensations in a fictional story for *The Atlantic Monthly* about a man named George Dedlow who lost an arm and both legs at war. The fictional character was said to awaken to consciousness in a hospital tent with a sharp cramp in his left calf. In disbelief when the attendant informed him that both his legs had been removed, George Dedlow threw off his blankets to discover in horror that both legs had indeed been amputated at thigh level. Due to a large response, great demand and generous donations Mitchell (1871) later published a non-fictional account based on the experiences of soldiers he treated after the American Civil War. The effort to define the illusions of missing limbs stirred a new interest in these phenomena and gave birth to the research with which we are familiar. From the work of Cronholm (1951), who first scientifically described referred sensations, to Ramachandran (1993), who introduced the possible neural correlates underlying these sensations, research in this field has come a long way from assuming that the cause of phantom pain lies stump neuromas (Kallio, 1950) to neuroimaging the cortical difference between amputees with pain and those without it (Flor *et al.*, 1996). Cognitive neuroscience has also progressed from taking for granted that people who are missing a limb from birth do not experience phantom sensations (Simmel, 1961) to showing the central workings and perceptual phantom experiences of these individuals (Brugger *et al.*, 2000). It is this modern research that is the focus here and this literature will be reviewed henceforth.

1. 2. Who, when, where and what?

1. 2. 1. Who? Phantom limb sensations are most commonly acquired after loss of a limb due to traumatic injury, such as road traffic accidents and war wounds (e.g. Johansen, Daines, Howey, Helfet and Hansen, 1990), or chronic vascular diseases, such as diabetes or gangrene (e.g. Bild *et al.*, 1989). Amputations resulting from cancer, infection, birth defects and other diseases also have been associated with phantom sensations (e.g. Krane and Heller, 1995). Of those who undergo amputation, anywhere from 70% to 100% are reported to

experience some form of sensation in the once-present limb (Wartan, Hamann, Wedley and McColl, 1997; Richardson, Glenn, Nurmikko and Horgan, 2006; Giummarra *et al.*, 2010) regardless of the event causing the limb to be removed (Jensen, Krebs, Nielsen and Rasmussen, 1983; Sherman and Sherman, 1983; Kratz *et al.*, 2010). Congenital phantom sensations also have been found in people born with a missing limb (Valentin, 1836; Wilson, Swinyard and Wilson, 1962; Brugger *et al.*, 2000), but the incidence of such cases is much lower at approximately 20% (Melzack, Israel, Lacroix and Schultz, 1997). The removal of other body parts has also been found to lead to phantom sensations (Brena and Sammons, 1979; Ovesen, Kroner, Ornsholt and Bach, 1991; Aglioti, Cortese and Franchini, 1994; Fisher, 1999; Soros, Vo, Husstedt, Evers and Gerding, 2001; Ramachandran and McGeoch, 2008), and the body part need not even be removed for phantom sensations to occur, such as in spinal cord injury, paraplegia or nerve avulsion (Sweet, 1975; Melzack and Loeser, 1978; Malin and Winkelmuller, 1985; Garcia-March *et al.*, 1987; Siddall, McClelland, Rutkowski and Cousins, 2003). Although there seem to be more male than female amputees (Sherman and Sherman, 1985), probably due to differences in risk-taking behaviour and lifestyle, differences are seldom found between the genders in phantom limb sensations (Jensen, Krebs, Nielsen and Rasmussen, 1984; Sherman and Sherman, 1985; Katz and Melzack, 1990; Kooijman, Dijkstra, Geertzen, Elzinga and van der Schans, 2000).

1. 2. 2. *When?* In approximately 50% of all amputees, the onset of phantom limb sensations occurs within the first 24 hours after amputation and by eight days after amputation 84% of patients experience phantom sensations (Jensen *et al.*, 1983). Yet delays of phantom sensation onset of up to 30 years also have been reported (Sunderland, 1978). Duration of phantom sensations are variable across patients (Sunderland, 1978), but both those painful in nature and not generally tend to decrease with time (Melzack, 1990; Pezzin, Dillingham and MacKenzie, 2000). Houghton, Nicholls, Houghton, Saadah and McColl (1994) found that the intensity of phantom pain reported by amputees decreased from a median of 4/10 (moderate) immediately after amputation to 1/10 (slight) five years later. Similarly, the frequency of phantom pain occurrences decreases significantly over the first six-month period (Nikolajsen, Ilkjaer, Kroner, Christensen and Jensen, 1997).

1. 2. 3. *Where?* When investigating differences in the location of the phantom, research often draws a distinction, but rarely finds a difference, between upper- and lower-

limb amputees (e.g. Raichle *et al.*, 2008), above- and below-joint amputations (e.g. Jensen *et al.*, 1983) and dominant and non-dominant lost limbs (e.g. Kooijman *et al.*, 2000). That said, differences are sometimes found. For example, Davidson, Khor and Jones (2010) showed that upper-limb amputees were more likely to suffer long-lasting and severe pain after amputation than lower-limb amputees; Giummarra *et al.* (2010) reported that proximal amputations were associated with higher degrees of telescoping, abnormal limb postures and less frequent prosthesis use; and Shukla, Sahu, Tripathi and Gupta (1982) observed that phantom sensations were more frequent for right arm amputation when compared to left arm amputation in amputees born right-handed. However, such findings are few and far between and the results in such cases are often dependent on the methodologies used to collect and analyse the data. Findings of these sorts are of great interest to science, but it is of key importance when reporting such statistics to clearly detail the unique circumstances and explain possible interpretations of these.

1. 2. 4. *What?* The experience that a phantom limb remains proprioceptively present is only one of many perceptual phenomena associated with amputation (Giummarra *et al.*, 2010). Some patients describe their phantom limb as being stuck in a fixed position (Jackson, 1889; Ramachandran and Rogers-Ramachandran, 1996), whilst others report full or partial mobility in the limb (Ramachandran and Hirstein, 1998). Although research on phantom mobility is limited, reports suggest that for some the movement capacity of the phantom may only be of instinctive automatic nature, such as reflexively pulling away from danger (e.g. Shukla *et al.*, 1982), but others may have volitional control over their phantom limbs (Price, 1976). When in a fixed position the posture of the phantom often reflects the state of the limb when it was amputated (Katz and Melzack, 1990). For example, if the limb was deformed prior to amputation, the phantom limb may also be experienced as deformed (Browder and Gallagher, 1948). In 25 - 67% of amputees the phantom limb is said to be telescoped (Carlen, Wall, Nadvorna and Steinbach, 1978; Fraser, 2002; Richardson, Glenn, Horgan and Nurmikko, 2007; Giummarra *et al.*, 2010). Telescoping refers to the change in size of the phantom limb respective to its size pre-amputation (Weiss and Fishman, 1963). This most commonly refers to the shortening or shrinking of the forearm or calf so that the digits feel as though they are nearer to or inside the stump, but the lengthening and enlargement of phantom limbs is not unheard of (Jensen *et al.*, 1983). Telescoped phantoms are more apparent in those without phantom limb pain (Jensen *et al.*, 1983) and those who do not use a prosthetic limb (Mayer, Kudar, Bretz and Tihanyi, 2008).

1. 3. Relating to the current research

The remainder of this literature review and the following thesis papers focuses on three perceptual phantom phenomena not yet discussed here: 1) phantom limb pain, 2) mirror-touch synaesthesia, and 3) referred tactile sensations. The overview continues to cover each of these in turn as we describe possible explanations for phantom pain in the first section, then look into how the brain encodes perception for action and identify why such a system might come into consciousness after amputation, and ultimately explain what is meant by referred sensations and outline a generally accepted explanation for this. At the end of each segment the literature it examined is related to the aims and hypotheses of the thesis papers, and conclusions bridging all the papers together are drawn in the final section. Most of the literature reviewed is of data collected from amputees with acquired limb-loss, as this is largely the focus of the research papers, however when relevant the findings are related to and compared with data from cases of congenital phantom limbs.

2. Phantom pain: Interpreting pain from mind to brain

Nearly all amputees experience some form of phantom sensations at one point or another after their limb has been removed (Ramachandran and Hirstein, 1998). For 50-80% of these patients a degree of pain is associated with the phantom limb (Jensen and Nikolajsen, 1999) and stump (Sherman, Sherman and Parker, 1984). Of the amputees with painful phantom sensations, 70% persist to experience pain even after 25 years (Sherman *et al.*, 1984); yet overall the percentage of amputees with phantom pain does decrease with time (Jensen *et al.*, 1983; Jensen, Krebs, Nielsen and Rasmussen, 1985). The onset of pain in the phantom limb is normally immediate, but sometimes only emerges years after amputation (Nikolajsen and Jensen, 2001). Although phantom experiences have been reported in congenital cases of missing limbs (Melzack *et al.*, 1997), phantom *pain* in such individuals is rare (Flor *et al.*, 1998).

The pain is often described as stabbing, throbbing or cramping (Hill, 1999) or as resembling the quality of the pain prior to limb loss (Katz and Melzack, 1990). Rest, stress, weather and emotional disturbance have been linked to increased levels of phantom pain (Jensen *et al.*, 1983; Sherman and Sherman, 1985), as well as making attempts to use the limb that is not physically present (Giummarra and Bradshaw, 2011). Phantom pain does not seem to be affected by cause of amputation, body part amputated, sex, age or socioeconomic

background (Jensen *et al.*, 1983, 1985; Sherman and Sherman, 1985). Here the possible causes of phantom pain in amputees are outlined, from the psychological issues, to the peripheral nervous system, and to the cortical plasticity of the brain.

2. 1. Psychological hypotheses of phantom limb pain

2. 1. 1. Unconscious wishes and desires: Based on Freud's (1931) theory that during sleep thought-impulses reawaken dormant representations by deflecting back through psychic memory systems, Zuk (1956) proposed that the phantom limb is "a narcissistic desire to maintain the body's integrity in the face of a realistic loss or a rejection of symbolic castration of a body organ" (p. 510). The theory elaborated that in the loss of limb mobility caused by the physical loss of the limb, the regressive process is satisfied as the unconscious must interpret the current change in physical ability (or "morbid state"; Freud, 1931) based on suppressed memories and unconscious-motive wish-impulses. Painful phantom sensations are explained as caused by the unconscious desire to use the missing limb when the nerves at the stump are irritated or when this desire comes in conflict with the ability to adjust to the reality of having lost the limb (Zuk, 1956).

2. 1. 2. Psychological distress and denial: Higher levels of pain after amputation have been associated with increased affective distress (Desmond and MacLachlan, 2006) and post-surgical anxiety (Sucala *et al.*, 2010). Early theories suggested that phantom sensations are a normal psychological response to the fears and anxieties related to amputation; phantom pain evolves to help maintain the physical and psychological representation of the body (Kolb, 1954), or as a form of emotional denial that the limb has been lost (Simmel, 1959). Parkes (1972) compared the pain of having lost a limb to the intense emotional pain experienced after losing a spouse or sibling. In both cases of loss there is an initial period of shock or numbness that is accompanied by a denial of the affective reality. This is subsequently followed by anxiety and distress, in which the mourner makes conscious attempts to avoid reminders of the loss, and finally by a stage of depression or apathy, where the sufferer is disinclined to think about the future. Accordingly, the sensation of a phantom limb is much like the intense feeling, or even hallucination, that the lost person is present even years after bereavement (Rees, 1971).

2. 1. 3. *Individual differences in personality and coping strategies:* Amputees who experience phantom limb pain tend to score higher on visual analogue scales measuring the rigidity of their attitudes and their compulsive self-reliance than amputees with non-painful phantom limb sensations; yet no difference has been found between these two groups in perfectionism, pain sensitivity or external anxiety (Parkes, 1973). Undergoing amputation is associated with a multitude of life changes, and those with a rigid resistance to change may not be adaptable to these life changes. As such an intact, but painful, representation of the limb may result in the form of a phantom. Despite this, phantom limb pain in this study was not correlated with overt depression or difficulty in adjustment to the amputation (Parkes, 1973). This might have been because these amputees had compulsive feelings that they must continue relying on themselves despite their obvious need for help from others, as they tended to see dependence as a sign of weakness.

However, in later investigations of factors determining phantom pain, studies have found no evidence of relationships between phantom pain and personality disorders, psychological reactions to amputation or "rigidity" (Shukla *et al.*, 1982; Sherman, 1989; Katz and Melzack, 1990). According to findings by Hill (1993) phantom pain may rather be related to the amputee's particular strategy. People who responded to amputation with a helpless attitude experienced higher levels of phantom pain and distress than those who worked to keep distracted, or those who applied cognitive methods for coping with the loss (Hill, 1993). Similarly, Richardson *et al.* (2007) interviewed patients before amputation and six months after surgery, and found a positive correlation between passive coping strategies prior to amputation, such as "catastrophising", and the later development of phantom limb pain.

2. 1. 4. *Proprioceptive memories of pain:* In an intensive review, Katz and Melzack (1990) introduced a cognitive theory of phantom pain with a potential neural basis. Many studies have shown qualitative, frequency or intensity similarities between the pain experienced prior to amputation and the phantom limb pain (Jensen *et al.*, 1983, 1985; Grusser, Schachinger, Muhlnickel, Wolff and Flor, 1998; Rothmund, Grusser, Liebeskind, Schlag and Flor, 2004). Accordingly, pain receptors associated with the conscious experience of amputation (in traumatic amputees) and the pain persisting in the limb before amputation (in illness-related amputations) are set off in a way that the signals are stored and remembered as somatosensory memories. Such memories may have initially evolved to protect from repeated injury (Anderson-Barnes, McAuliffe, Swanberg and Tsao, 2009). It has

been hypothesised that once the pre-amputation pain representation has been established, it is strengthened every time the pain is experienced so that eventually it is activated when only some of its elements are present (Melzack, 1989; Katz and Melzack, 1990).

2. 2. Peripheral nerve damage and phantom limb pain

2. 2. 1. Neuroma formation and stump nerve stimulation: Noxious pain occurs when the body experiences direct injury or other unpleasant sensory input to tissues that contain nociceptors. Nociceptors are afferent neurons found in the skin, muscles, bones, blood vessels and joint tissues that normally respond to extreme mechanical, chemical or thermal stimulation (Basbaum and Jessell, 2000; Julius and Basbaum, 2001). The nociceptors that respond to extreme temperatures and intense pressure, A δ fibres, are thinly myelinated allowing them to conduct signals at a faster pace than the C fibres of polymodal nociceptors that have non-myelinated axons. When noxious pain causes transformations at the molecular and cellular level of the nervous systems it becomes neuropathic and maladaptive (Woolf and Mannion, 1999). Neuropathic pain is chronic and associated with physical problems, such as hyperalgesia, allodynia or spontaneous pain (Woolf and Salter, 2000), as well as emotional and sociological problems, which often become pain triggers (Hainline, 2011).

When a limb is severed the unmyelinated C fibre endings of the damaged polymodal nociceptors regenerate and sprout spontaneous connections. The new mass of axons becomes tangled as the axons cannot reconnect systematically and a swollen nodule of neurons is formed (see Figure 1). This is known as a neuroma, and when stimulated can cause an ectopic discharge release (Devor, Keller and Ellisman, 1990; Devor, Govrinlippmann and Angelides, 1993). Release of ectopic discharge sends unexpected impulses to the spinal cord resulting in neuropathic pain perceptions (Wall and Gutnick, 1974; Sherman, 1997). Such discharge may be brought about by physical stimulation of the stump by touch, pressure, local inflammation, oxygenation or change in temperature (Nystrom and Hagbarth, 1981). Discharge from neuromas may also occur spontaneously due to the nerve damage or emotional distress (Katz, 1992).

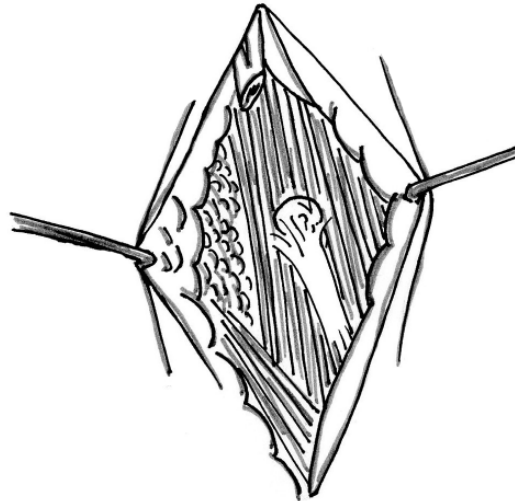


Figure 1: A tangled nodule of deafferented axons known as a neuroma.

In support of this hypothesis there is ample data that suggest a link between the frequency and intensity of stump pain and phantom pain (e.g. Sherman and Sherman, 1983, 1985). Mechanical stimulation of the stump can trigger phantom pain (Echlin, 1949; Nikolajsen, Ilkjaer and Jensen, 2000). On the contrary, applying local anaesthetic to the region (Livingstone, 1938, 1943), removing the neuromata by means of surgery (Kallio, 1950; Jensen and Rasmussen, 1994), or using beta-adrenergic blocking agents (Marsland, Weekes, Atkinson and Leong, 1982) reduces or eliminates phantom limb pain at least temporarily. However, albeit neuromata may contribute to painful sensations in the stump and phantom limbs, Nystrom and Hagbarth (1981) found that anaesthetic blockade of neuromata reduced stump pain but not phantom pain, and even when anaesthesia does have an impact on phantom limb pain it is not consistent across all amputees (Birbaumer *et al.*, 1997). Furthermore, phantom pain often occurs immediately after amputation and before the nociceptor axons have the opportunity to regenerate and form neuromata (Nikolajsen and Staehelin Jensen, 2000).

2. 2. 2. Spinal cord disinhibition: An alternative, or perhaps complementary, explanation for the origins of neuropathic pain, such as is seen in the case of phantom limbs, is found further up the sympathetic peripheral system, at the level of the spinal cord in the dorsal root ganglia (Nathan, 1983; Woolf and Mannion, 1999). The afferent nociceptors' axons terminate in the dorsal horns of the spinal cord, and the cell bodies of these neurons are contained in the dorsal root ganglia (Basbaum and Jessell, 2000; see Figure 2). The projections normally received in the dorsal horn are not all excitatory in nature. Some signals act as an

inhibitory "gate" that prevents the brain from interpreting a perception as painful when the body is not under threat (Melzack and Wall, 1965; Melzack, 1996). When the limb is severed and the nociceptor fibres are damaged the inhibitory signals to the spinal cord are lost resulting in ectopic discharge in the dorsal root ganglia (Moore *et al.*, 2002). This, in turn, results in increased levels of pain (Wall and Devor, 1983). As disinhibition occurs immediately with amputation, this might provide a better explanation for the instant manifestation of phantom limb pain than the theory of neuromata formation (Hill, 1999; Flor, 2002). Nevertheless, phantom limb pain has also been observed in individuals with no nerve damage, such as in paraplegia (Melzack and Loeser, 1978), and in individuals who have experienced a transection of the spinal cord (Riddoch, 1941; Melzack, 1992). This would indicate that although peripheral nerve systems may play a role in phantom limb pain, the phenomenon's original source is likely to lie in the central nervous system.

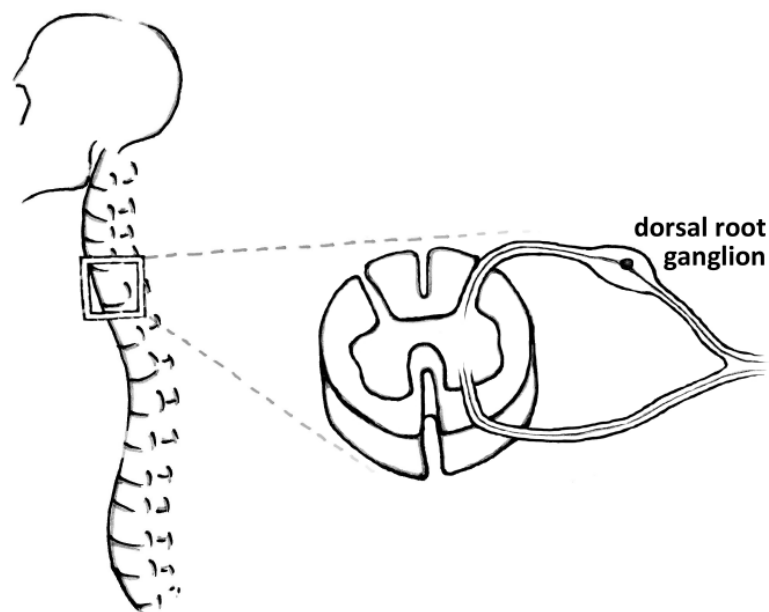


Figure 2: Axons from nociceptors terminate in the dorsal horns of the spinal cord and cell bodies are contained inside the dorsal root ganglia.

2. 3. Central factors in phantom limb pain

2. 3. 1. Pain in the neuromatrix: From as early as the 17th century Descartes (1637) argued that all sensations, including pain, are located in the brain. He claimed that the mere existence of the phantom limb was evidence for the brain activity normally associated with the

missing limb. However, it wasn't until late in the 20th century that Melzack (1990, 1992) proposed the first neural hypothesis to explain the origin of such sensations and pain. His theory suggested that the brain contains a genetically innate matrix of neural connections that not only responds to sensory stimulation, but also generates a continuous pattern of neural activity. Melzack termed this matrix the "neurosignature" as it represents the body as whole and as belonging to one's self. Therefore, despite the peripheral removal of a limb in amputation, the sensation of the limb generated by the brain remains intact (Melzack, 1990, 1992). Phantom pain is explained as resulting from the loss of sensory input to the neuromatrix from the missing limb. Burning pain may be the consequence of disinhibited bursting activity through the spinal cord (also supported by Sherman, 1984), whilst cramping or shooting pain could be the outcome of attempts made by the neuromatrix to move the muscles of the absent limb.

2. 3. 2. Reorganisation in the primary somatosensory cortex: In line with Melzack's (1990, 1992) theory of a central neuromatrix, Ramachandran (1993) also postulated that the source of phantom limb pain could be found in the brain. Ramachandran (1993), however, attributed the pain to erroneous cross-wiring in the plastic reorganisation of the primary somatosensory cortex. Magnetoencephalographic and neuromagnetic imaging techniques have shown that when the cortex no longer received sensory input from the missing limb, the areas of the brain that were formally responsible for interpreting the limb's sensations began to respond to other parts of the body (e.g. Yang, Gallen, Schwartz and Bloom, 1993; Flor *et al.*, 1995a). This diverted sensory activation has subsequently been associated with sensations in the phantom limb. Phantom pain has been suggested to be the consequence of an "accidental" cross over in the nerve fibres so that touch to the new input regions of the body is experienced as pain (Ramachandran, 1993).

However, Ramachandran's (1993) proposal did not explain how or why phantom pain becomes spontaneous or chronic. Although he explained that the pain-inducing touch may not be noticeable as it is overshadowed by the amplified pain signals, according to the theory pain would only be experienced when the referring body parts are being stimulated. Further investigation of such referred sensations from the body to the phantom limb discovered that cortical reorganisation was only evident when painful phantom sensations were induced by noxious stimuli, and not other forms of tactile stimulation whether resulting in phantom pain or not (Grusser *et al.*, 2001). Birbaumer, Flor, Lutzenberger and Elbert (1995) found that

people with chronic back pain were facilitated in processing noxious stimuli as early as 70-125 milliseconds after their presentation. They proposed that neuropathic pain involves widespread and permanent changes in the cortical processing of pain. The magnitude of chronic phantom pain has since been found to strongly correlate with the extent of central plasticity in the function of the primary somatosensory cortex (Flor *et al.*, 1995a; Lotze, Flor, Grodd, Larbig and Birbaumer, 2001; see Figure 3). Such cortical reorganisation is not found in amputees who experience non-painful phantom limb sensations (Flor *et al.*, 1996), or individuals with congenitally missing limbs (Flor *et al.*, 1998). This, hence, suggests that cortical reorganisation may only occur in amputees who experience explicit phantom pain sensations. Further details of topographical reorganisation in the cortex and their non-painful implications are discussed later (see section 4. 2. 2.).

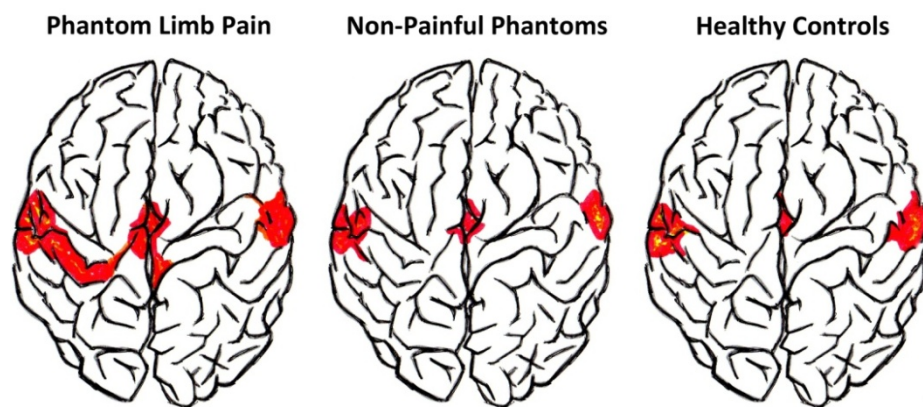


Figure 3: Cortical activity during lip pursing activity in amputees with phantom limb pain, amputees with non-painful phantom limb sensations and healthy control participants. In the patients with phantom limb pain lip movement activates the amputated hand's cortical representation in the primary somatosensory cortex (adapted from Lotze et al., 2001).

2. 3. 3. Synaesthesia for pain: In inspecting the role of visual input on phantom limb sensations, Ramachandran and Rogers-Ramachandran (1996) introduced a potential cure for some forms of phantom pain. Their "virtual reality box", now known as a mirror-box, consisted of a mirror placed vertically in a box so that when the amputee's intact hand was placed in the box its reflection was superimposed onto the proprioceptive location of the phantom hand. The study revealed that in upper-limb amputees who reported their phantom limb to previously have been paralysed, receiving visual feedback that the phantom limb is intact allowed them to move their phantom limb. Four out of five amputees were even able to unclench painful fist spasms, and for one patient continuous practice made the phantom limb

disappear altogether. For four patients seeing their intact limb being touched evoked a touch sensation in the same location on the phantom limb; the authors described this as "a curious form of synaesthesia" (Ramachandran and Rogers-Ramachandran, 1996, p. 377).

Ramachandran and Rogers-Ramachandran (1996) laid the groundwork for exploring the role of vision and synaesthesia in phantom pain perception, but only recently has this been taken a step further by the proposal that one neural system, "the mirror system", is responsible for both observed pain by amputees and their experience of phantom limb pain (Giummarra, Gibson, Georgiou-Karistianis and Bradshaw, 2007; Fitzgibbon *et al.*, 2010a; Fitzgibbon, Giummarra, Georgiou-Karistianis, Enticott and Bradshaw, 2010b; the mirror system and its role in non-painful phantom experiences is discussed in section 3. 2.). Giummarra and Bradshaw (2008) discovered a phenomenon, termed "synaesthesia for pain", in which seeing another person who is experiencing pain caused the amputee to experience a similar quality of pain in their phantom limb. A key difference between this form of synaesthesia in amputees and that described previously is in the locus of the inducing stimulus. Ramachandran and Rogers-Ramachandran's (1996) report of synaesthesia occurs in intra-personal space, i.e. it was triggered by vision of the amputee's own body in their own bodily space. However, the synaesthesia introduced by Giummarra and Bradshaw (2008) took place in inter-personal, i.e. it was triggered by vision of someone else's body in extra-personal space.

Fitzgibbon *et al.* (2010b) further hypothesised that such synaesthesia for pain is modulated by hyper-sensitivity to pain cues, as is experienced in the peripheral and central nervous systems following injury. Normally, this extra sensitisation to pain is adaptive as it allows the wound to avoid further damage and repair itself, as well as reducing the pain threshold around and beyond the injured site. It is possible that such heightened sensitivity caused by amputation is maintained through cognition, emotion and attention; and that the damage caused to the mirror system causes a disinhibition in the empathic processing of other people's pain (Fitzgibbon *et al.*, 2010b). Albeit unlikely that the mirror system is the sole cause of phantom limb sensations, it might be a contributing factor in eliciting the sensations and an environmental determinant of individual differences in phantom pain sensations.

2. 4. Relating to the current research

Whether by means of erroneous cross-wiring (Ramachandran, 1993) or systematic reorganisation of the primary somatosensory cortex (Flor *et al.*, 1996), it is generally accepted

that the main source of phantom pain lies centrally in the brain. What is less agreed upon is whether certain attributes of the amputation or characteristics of non-painful phantom phenomena are associated with phantom pain. Every large-scale questionnaire study has come across slightly different results and has drawn somewhat different conclusions (Jensen *et al.*, 1983; Sherman and Sherman, 1983; Jensen *et al.*, 1985; Sherman and Sherman, 1985; Houghton *et al.*, 1994; Kooijman *et al.*, 2000; Richardson *et al.*, 2007). As such, Paper 1 aims to investigate the incidence of phantom pain frequency and intensity, and examine the environmental factors which may trigger such sensations in the current sample of amputees. The paper looks at differences between amputees based on physical amputation details, such as cause of amputation, body part removed, level of amputation, dominance of lost limb and sex. Amputees are also divided on the basis of their non-painful perceptual phenomena, such as presence of synaesthesia, telescoped perceptions, mobility of the phantom and embodiment of prosthetic limb.

3. Observing actions: One system for perception and action

Halligan (2002) emphasised the importance of studying phantom limb phenomena in the context of the brain and body schema. Body schema, a term first proposed by Head and Holmes (1911-12), has been recently defined as "a dynamic representation of the relative positions of body parts derived from multiple sensory and motor inputs (e.g. proprioceptive, vestibular, tactile, visual, efference copy) that interacts with motor systems in the genesis of actions" (Schwoebel and Coslett, 2005, p. 543). The persistent experience of a phantom limb has classically been considered to be a perceptual memory of a formerly fully functioning part of the body (Katz and Melzack, 1990), i.e. a preserved central representation which survives in the face of peripheral damage (Brugger *et al.*, 2000). However, up to 20% of people born with a missing limb also experience phantom sensations despite never having had a limb to "remember" (Melzack *et al.*, 1997). Brugger *et al.* (2000) described the case of a woman who, despite being born with no upper- or lower-limbs, experienced vivid phantom sensations of both arms and legs. The authors suggested that the woman had a normal body schema which included the missing body parts. Consistent with this, functional magnetic resonance imaging revealed neural remapping of the shoulder representations into the region that would normally represent the hand in the primary somatosensory cortex (Brugger *et al.*, 2000). Giummarra, Gibson, Georgiou-Karistianis and Bradshaw (2007) proposed that there must be something external, perhaps visual, influencing phantom sensations that goes beyond a

remembered limb or the internal changes that take place in the cortex. Here we describe evidence for a single network of neurons responsible for both the perception and execution of action that may play a role in the formation and consolidation of phantom limb sensations in amputees and cases of congenitally missing limbs. We also provide an overview on budding research into acquired mirror-touch synaesthesia in amputees, a condition in which observing other people's actions can trigger involuntary phantom sensations (Henderson and Smyth, 1948; Melzack *et al.*, 1997) and in extreme cases pain (Fitzgibbon *et al.*, 2010a; 2010b).

3. 1. Perception of biological motion is special

3. 1. 1. Classic methods of studying biological motion: In order to link perception to action the extra-striate visual system must process biological stimuli differently to other moving objects, and interpret the observed actions of others in terms of those we can produce ourselves (for overview see Blakemore and Decety, 2001; Shiffrar and Pinto, 2002).

Evolutionarily, the skill to distinguish the movements of others from the environment is vital for animal survival, and without it we would be lost at understanding the intentions, emotions and abilities of those we encounter. In the very first few hours of life, neonates already possess the ability to imitate the facial and manual gestures of adults, showing an understanding of the likeness of others to themselves (Meltzoff and Moore, 1983; Reissland, 1988). By the age of 5 months, infants can differentiate between types of human gait, but not of animal gait (Pinto, 2006), suggesting that there is a unique quality for the perception of human biological motion specifically.

Only minimal visual information is necessary for recognition of human biological motion. Johansson (1973) introduced a 'point light' animation technique whereby human motion could be studied without the confounding variance found in human shape and form (for a review see Blake and Shiffrar, 2007). In a video of light markers attached to the head and joints of a body moving in the dark, people could rapidly and effortlessly detect human movement (biological motion), and differentiate this from displays in which the same number of dots move at random (non-biological motion; Johansson, 1973). Further research has shown that people were even able to detect the specific action (Dittrich, 1993), sex (Mather and Murdoch, 1994), identity (Troje, Westhoff and Lavrov, 2005), direction of gait (Mather, Radford and West, 1992), sexual orientation (Johnson, Gill, Reichman and Tassinari, 2007), intention to deceive (Sebanz and Shiffrar, 2009) and facial expression (Bassili, 1978) of point light motion displays, and that these, like other stimuli in visual perception, were subject to

rules of inversion (Sumi, 1984). Single-cell recordings in the macaque monkey have revealed neurons in the anterior region of the anterior superior temporal polysensory area that responded selectively to point light biological motion (Oram and Perrett, 1994, 1996). Similarly, functional magnetic resonance imaging recordings demonstrated the human equivalent region, the superior temporal sulcus, was also activated when observing biological point light animation (Vaina, Solomon, Chowdhury, Sinha and Belliveau, 2001; Beauchamp, Lee, Haxby and Martin, 2003).

Other techniques for examining the human ability to detect biological kinematics rely on methodologies completely devoid of motion. Using functional imaging, Kourtzi and Kanwisher (2000) found heightened activity in MT/MST, cortical areas normally responsible for the visual processing of physical motion, whilst participants viewed photographic stills that implied motion, such as a man throwing a ball, when compared to photographs that did not imply motion, such as a man standing still or a picture of a building. These brain regions not only perceive biological motion when observing static photographs of actions, but similar activation is found when simple line drawings of instability are presented in the form of Hokusai Manga (Osaka, Matsuyoshi, Ikeda and Osaka, 2010), and such activity is modulated by the implied speed of the suggested motion (Williams and Wright, 2009).

A more commonly used approach for measuring the role of form in human kinematics independent of motion was put forward by Shiffrar and Freyd (1990). Participants were presented with two still images that were identical with the exception of the location of one limb relative to the rest of the body. The images rapidly alternated to produce the visual illusion of apparent biological motion. When presented at short interstimulus intervals (ISIs), e.g. 150-350 milliseconds, the apparent limb movement took the shortest route between the two limb positions, regardless of whether or not this route of motion was anatomically possible. At longer ISIs, e.g. 550-750 milliseconds, the apparent motion of the limb took the anatomically and physically possible path of movement even if this was not the most direct route. Shiffrar and Freyd (1990) explained that the reason for this is that in order to interpret the realistic biological motion the brain needed the amount of time that is necessary to actually carry out the movement. Moreover, these findings were not extrapolated to the equivalent perception of apparent object motion (Chatterjee, Freyd and Shiffrar, 1996; Shiffrar and Pinto, 2002). In the case of objects, regardless of the ISI duration, participants tended to perceive the shortest route between the two image positions, suggesting that object movement and human movement were processed differently. These findings were supported by a study that used positron emission tomography to show that the premotor and inferior

parietal cortex exhibited heightened activation for long ISIs, when the biologically possible route was perceived, but not at short ISIs, when the observer perceived the physically impossible (Stevens, Fonlupt, Shiffrar and Decety, 2000). In a similar vein, cortical motor activation was specific to human motion relative to object motion (Stevens *et al.*, 2000).

3. 1. 2. Perception and action share a mental representation: The theory of event coding suggests a framework in which late event perception and early to-be-executed event production are linked by "a common representational domain" (Prinz, 1997; Hommel, Musseler, Aschersleben and Prinz, 2001, p. 849). Behavioural support for the notion of a shared mental representation, or body schema, for both action perception and action planning comes from studies demonstrating facilitation when detecting familiar actions or interference whilst executing and observing concurrently. Experiments involving the point light animation technique have revealed that participants were better at detecting their own biological motion than that of others (Beardsworth and Buckner, 1981; Loula, Prasad, Harber and Shiffrar, 2005). Similarly, people were capable of recognising their own drawing trajectories based purely on kinematic cues (Knoblich and Prinz, 2001), and were better at predicting the outcome of an arrow throw when observing themselves rather than another person's throw (Knoblich and Flach, 2001). Not only does familiarity facilitate action recognition, but so do the observer's activities during action perception. For example, Reed and Farah (1995) found a heightened ability in detecting change in an observed body posture when participants were holding their own body in the same posture, suggesting that there is a common representation of both action execution and perception.

However, executing an action whilst observing it does not always lead to task facilitation. Hamilton, Wolpert and Frith (2004) had participants observe an actor lifting a box whilst holding a similar box. The observed box was judged as lighter when lifting a heavier box and as heavier when lifting a lighter box (Hamilton *et al.*, 2004). In a similar manner, another study found that participants who walked, as opposed to standing still or cycling, performed worse on a gait-speed discrimination task, indicating that carrying out the same action as was being observed led to an interference in task performance (Jacobs and Shiffrar, 2005). Moreover, carrying out an action was only disrupted when observing the same action being executed by another human, and not when it was executed by an obviously mechanical robot (Kilner, Paulignan and Blakemore, 2003). Although it appears that sometimes the relationship between action observation and execution leads to facilitation, and at other times it leads to

inhibition, it is clear that there is a link between the two processes which indicates that it is highly likely that the two rely on the same representational system. Reed and McGoldrick (2007) proposed that when there is only a limited amount of time to process the stimuli, executing the action whilst observing it leads to an inhibitory effect; whereas given enough time to fully process the stimuli, concurrent action production can facilitate the cognitive analysis.

3. 1. 3. The effects of brain abnormalities on body perception: Further evidence for a shared mental representation for action and perception comes from the study of individual cases in which the system is disrupted resulting in the lack of an integrated body schema. If action perception relies on the same system as action planning and execution, then individuals with motor impairment, due to congenital abnormalities or brain damage, should not show the same facilitation or inhibitory effects as the rest of the population. For example, individuals with Down's syndrome show poorer performance in detection of human biological motion in point light animations than age-matched controls (Virji-Babul, Kerns, Zhou, Kapur and Shiffrar, 2006). Children with autism also show an increase in point light animation errors (Kaiser, Delmolino, Tanaka and Shiffrar, 2010), which may be linked to structural abnormalities of the superior temporal sulcus (Boddaert *et al.*, 2004) and perhaps dysfunction in the system for mirroring perception and action (Perkins, Stokes, McGillivray and Bittar, 2010). By means of electroencephalography most people show suppressed mu and beta oscillations over the sensorimotor cortical regions during action execution and somatosensation, respectively (Pfurtscheller, Neuper, Andrew and Edlinger, 1997; for a review see Pineda, 2005). These rhythms are not only suppressed during action production, but are also significantly reduced during action observation (Muthukumaraswamy and Johnson, 2004; Muthukumaraswamy, Johnson and McNair, 2004) and imagination (Pfurtscheller and Neuper, 1997; Pfurtscheller, Brunner, Schlogl and da Silva, 2006). This suppression for both action production and action perception is claimed to reflect a selective measure of an integrated representation for perception and action (Oberman *et al.*, 2005). Individuals with autism show normal suppression when carrying out an action, but not when observing others doing the same action (Oberman *et al.*, 2005; Honaga *et al.*, 2010), suggesting a malfunctioning system for linking perception and action, as well as a deficient theory of mind (Pineda and Hecht, 2009).

In hemiplegia the person experiences paralysis or paresis to one side of the body as a consequence of a brain lesion in the contralateral brain hemisphere. The study of hemiplegia

and related disorders has also provided insight into the notion of a unified body schema for perception and execution by allowing for the investigation of the consequence to one when the other is impaired. Such lesions are usually acquired by stroke but can sometimes be congenital. The question here is, to what extent are hemiplegics' bodies aware of their motor deficits and does this deficit have an impact on their motor perception? Sandifer (1946) described cases where due to hemiplegia the patients had lost their motor abilities, yet remained in denial of this and struggled to accept the paretic limb as their own. This is known as anosognosia, and is found in hemiplegics with premotor cortex damage, but not in those without it (Berti *et al.*, 2005). According to Frith (2000) a secondary body representation of both executed and imagined actions is stored in the premotor cortex; therefore, damage to this area may cause an inability to distinguish between these. Serino *et al.* (2010) compared stroke patients with hemiplegia to those without it on point light animation tasks. They found that the hemiplegics showed poorer performance on action recognition when observing actions produced by the arm equivalent to the paretic arm when compared to observing actions produced by the non-paretic arm. Thus, it seems that action perception suffers when action execution is compromised by a contralateral lesion (Serino *et al.*, 2010), and the ability to interpret biological motion is dependent on the ability to execute such motion.

3. 2. The mirror-system

3. 2. 1. Mirror neurons for perception of action: When observing a football game our hearts start to race, when witnessing another vomit we feel sick to our stomachs, and when seeing a person lightly dressed on a cold winter's day we give off a shiver. How we comprehend what another is experiencing, feeling and thinking at such an intrinsic level can be explained by the mirror system. The neurons in this system fire not only when a goal-directed action is performed, but also during the observation of the same action being executed by another person (Gallese, 2001). Mirror neurons were first discovered in the macaque during a single-cell recording experiment which demonstrated that cells in area F5 of the ventral premotor cortex discharged not only when executing an action, but also when observing another monkey or experimenter carry out a similar action (di Pellegrino, Fadiga, Fogassi, Gallese and Rizzolatti, 1992; Gallese, Fadiga, Fogassi and Rizzolatti, 1996; Rizzolatti, Fadiga, Fogassi and Gallese, 1996). Transcranial magnetic stimulation to the primary motor cortex revealed a similar result in humans, namely a selective increase in motor-evoked potentials

was found when the participants observed actions that if carried out would involve the very muscles recorded (Fadiga, Fogassi, Pavesi and Rizzolatti, 1995).

Albeit biological motion can be perceived in the absence of form, as exemplified by point light animations (Blake and Shiffrar, 2007), and in the absence of continuous motion, as exemplified by apparent biological motion (Shiffrar and Freyd, 1990), it is the integration of form and motion that allows us not only to perceive, but also to interpret the actions of others with respect to our own motor capabilities and intentions (Oram and Perrett, 1994, 1996; for a recent review see Shiffrar, 2011). Decety and Grezes (1999) discussed the link between kinematic perception and understanding of action production in terms of the dorsal and ventral extra-striate pathways originally introduced by Ungerleider and Mishkin (1982). The ventral pathway, projecting from the primary visual cortex via V2 and V4 to the inferior temporal cortex and to the anterior superior temporal sulcus, deals with object recognition and identification on a slow-processing conscious level, i.e. form perception. The dorsal visual pathway, projecting from the primary visual cortex via V2 and V3 to MT/V5 and then to the posterior parietal cortex and superior temporal cortex, is responsible for the guidance of egocentric actions in real-time, including motion perception. The dorsal and ventral streams converge in the anterior superior temporal sulcus (superior temporal polysensory area in the macaque) and premotor cortex (for a review see Farivar, 2009). These are the areas activated when observing point light animations and rapidly alternating still images (Stevens *et al.*, 2000; Vaina *et al.*, 2001; Beauchamp *et al.*, 2003; Saygin, 2007). This suggests that these cortical areas play a key role in the overall perception and understanding of biological motion (Grossman, Jardine and Pyles, 2010). The areas where the dorsal and ventral streams converge are also strongly associated with mirror neuron activity (Rizzolatti, Fabbri-Destro and Cattaneo, 2009; Molenberghs, Brander, Mattingley and Cunnington, 2010).

A number of studies have shown that mirror neurons don't merely respond to all elements of a certain action, but that they rather respond to the intentions of the person performing the action. For example, Rizzolatti and Craighero (2004) discovered that only a third of mirror neurons in the macaque responded to observing strictly the action executed; the remainder fired in response to logically related or complementary actions. The reason for this is perhaps to support cooperative behaviour amongst social beings and establish an assumed understanding of joint intentions (Newman-Norlund, van Schie, van Zuijlen and Bekkering, 2007; Bekkering *et al.*, 2009). Similarly, mirror neurons only fire in response to goal-orientated actions and not objectless pantomimed actions (Rizzolatti *et al.*, 1996). However their properties can be shaped with experience (Umiltà *et al.*, 2008). For example,

mirror neurons that respond to observing a precision grip did not originally fire in response a similar grip executed with pliers (Rizzolatti and Arbib, 1998). Yet after years of observing humans using pliers in experiments, Ferrari, Rozzi and Fogassi (2005) found that approximately 20% of mirror neurons in area F5 of the macaque subsequently showed a response to tool use. This seems to indicate that with time the monkeys learnt that the same goal can be achieved by different means, but that the intention remains the same.

Perhaps the best evidence for the mirror system's role in social understanding of intention comes from a study where the macaque observes the same stimulus in two conditions and only the experimenter's intention differs (Umiltà *et al.*, 2001). The monkeys would either watch an object being placed in front of them or an object-less pantomime of this action, and subsequently see the experimenter reach towards that location. In the test conditions the grasp motion at the end of the action, i.e. the critical part for eliciting a response in full view, was occluded by a screen so that both the real-action and pantomime conditions were visually identical. Despite this, half of the mirror neurons fired in response to the condition where they knew the object was present but not in response to the pantomime condition (Umiltà *et al.*, 2001). The authors concluded that the representation of the action was brought about by the macaque's expectation or knowledge of the action's outcome, as the neurons seemed to perceive the same visual information in two different ways.

3. 2. 2. Empathy and mirror-touch synaesthesia: In humans, much of research into the mirror system has focused on empathy and the role that such a system plays in understanding not only the intentions, but also the feelings, thoughts and behaviours of other people (for a recent review see Iacoboni, 2009). In addition to motor action perception, functional neuroimaging studies have revealed that the mirror system was involved in the perception of touch (Keysers *et al.*, 2004) and pain (Singer *et al.*, 2004). When seeing another person being touched or sensing pain our brains "mirror" the neural activity of the person being observed, leading to an empathic understanding of what the other is going through (Bufalari, Aprile, Avenanti, Di Russo and Aglioti, 2007; Iacoboni, 2009). For example, Singer *et al.* (2004) measured the brain activity of volunteers when they experienced a painful stimulus and when they were present in the room when a loved one received a similar painful stimulus; they found activity in the rostral anterior cingulate cortex, the brainstem, the cerebellum and bilaterally in the anterior insulae for both self-perceived pain and when receiving a signal that someone they cared for was in pain. Similarly, the left anterior insula, which responds

maximally to disgusting gustatory and olfactory stimuli (Small *et al.*, 2003), was also activated by the sight of disgusted facial expressions of others (Phillips *et al.*, 1997; Krolak-Salmon *et al.*, 2003). This further suggests that the mirror system allows us to emulate the experiences of other people. Electroencephalographic mu suppression, associated with mirror system activity (Holz, Doppelmayr, Klimesch and Sauseng, 2008), is enhanced in individuals who perform highly in the perspective taking subscale of the interpersonal reactivity index (Woodruff, Martin and Bilyk, 2011). This has been taken to support the notion that mirror activity is indeed related to empathy.

For individuals with mirror-touch synaesthesia observing another person being touched induces a vivid experience of a concurrent tactile stimulation on their own bodies (Banissy *et al.*, 2009). In these people the interaction between action and observation is more vigorous, and empathy is more enhanced than in the general population (Blakemore, Bristow, Bird, Frith and Ward, 2005; Banissy and Ward, 2007; Banissy, Kadosh, Maus, Walsh and Ward, 2009). In synaesthesia a certain characteristic of a perceptual stimulus, the inducer, causes a conscious experience in a different modality or different attribute of the same modality, the concurrent (Grossenbacher and Lovelace, 2001). Blakemore *et al.* (2005) reported the first case of mirror-touch synaesthesia, and found that this condition was associated with higher activation than non-synaesthetic controls in the somatosensory cortex and left premotor cortex when observing faces being touched. Bilateral activation of the anterior insulae was also present in the synaesthete, but not in the control participants. As such, the authors proposed that mirror-touch synaesthetic experiences might rely on the same mirror system that is present in us all, but that in synaesthesia a genetic difference (Asher *et al.*, 2009) may over-activate the system and bring these cross-modal interactions into consciousness (Ward, Huckstep and Tsakanikos, 2006).

3. 3. The Mirror System in Amputees

Brugger *et al.* (2000) were first to speculate that the mirror system may provide answers for some unexplained phenomena experienced by amputees. They proposed that we may be born with an innate body schema, equivalent perhaps to Melzack's (1990, 1992) neuromatrix, but that this can be shaped by our experiences within our bodies and our bodies' experiences within the environment. When a body part is missing, either congenitally or by means of acquired amputation, the internal representation of the limb may remain intact because the mirror system is able to infer the sensation of action execution from experience

with action observation. As such the mirror system could be responsible for the phantom sensations of people born with a missing limb, as their bodies not are experienced in planning actions with a non-existing limb (Brugger *et al.*, 2000). Price (2006) extended this theory by suggesting that the body schema is based on environmental sensory input and proprioceptive feedback, but that the development of this schema begins in utero, when the environmental sensory input would be indicative of a missing member. The body representation we are subsequently born with is consolidated in the first decade of life by means of the mirror system and prosthetic use. Thus congenital phantoms may be dependent on the stage at which the brain becomes aware that a body part has failed to develop (Price, 2006).

After a limb has been amputated some people find they experience a vivid sensation in their phantom limb when they observe another person being touched (Henderson and Smyth, 1948; Melzack *et al.*, 1997) or see someone in pain (Fitzgibbon *et al.*, 2010a; 2010b). Appreciating the possible role of the mirror system in phantom limb sensations is vital for understanding why mirror-touch synaesthesia may arise in amputees after the loss of a limb. Fitzgibbon *et al.* (2010a) provided a preliminary investigation into this form of synaesthesia in amputees and reported an incidence of 16.2% in a sample of 74 amputees. In a review of the topic, the same group proposed that the mirror system in amputees may be disinhibited by the painful or traumatic experience that caused the amputation, allowing pain empathy for others to reach supra-threshold levels as a byproduct of hypervigilance to pain cues (Fitzgibbon *et al.*, 2010b). Research in this field is still in its embryonic stages and not much else is known about the neural correlates associated with acquired mirror-touch synaesthesia or what the implications of this research may be for relief from phantom pain and other phantom phenomena.

3. 4. Relating to the current research

The current research aims to provide further insight into the processes that underlie acquired mirror-touch synaesthesia, and shed light on what stimuli trigger these sensations in amputees. Paper 2 investigates whether the item being touched, i.e. body, dummy or object, or what it is being touched with, e.g. paintbrush or knife, influences the triggering of mirror-touch synaesthesia in amputees. Individual differences between amputees who report synaesthesia and those who do not are also explored. In Paper 3 we examine the differences between amputees and the general population in the processing of observed actions. Funk, Shiffrar and Brugger (2005) tested two cases, each with two congenitally missing upper limbs,

on the perception of apparent biological motion. They concluded that phantom sensations are necessary for a normal pattern of results to emerge, as phantom sensations are indicative of an intact body schema. Paper 3 aims to take this research a step further by examining particular attributes of the phantom sensations, namely the mobility and solidity of the phantom limb. Moreover, self versus other perspectives, body versus object stimuli and upper- versus lower-limb images are compared.

4. Cortical remapping: Tactile acuity and systematic mislocalisation

After the loss of an arm, upper-limb amputees often report with astonishment the feeling of touch to the phantom fingers or palm when their face or stump are stimulated (Ramachandran, Rogers-Ramachandran and Stewart, 1992a; Ramachandran, Stewart and Rogers-Ramachandran, 1992b; Halligan, Marshall, Wade, Davey and Morrison, 1993). As for lower-limb amputees, Ramachandran (1993) described a case where during sexual arousal a man felt his orgasm spread into the phantom foot so that it felt as though his phantom leg would explode at climax. Upon scientific investigation of such reports, Aglioti, Bonazzi and Cortese (1994) found that stimulation of skin sites on the stump of lower-limb amputees produced referred phantom sensation in the foot and toes. Similarly, one of our patients described that when she urinated she often felt as though liquid was trickling down the side of her leg despite the lower limb being amputated at hip level, and another found that his phantom arm was no longer uncomfortably cold after we recommended he try to wrap a scarf around his face during brisk weather. Such referral of experiences from adjacent body parts to the phantom limb after the peripheral elimination of sensory input to the central nervous system is known as "referred sensation". These are also found in patients with chronic pain (Katz and Melzack, 1987), stroke (Turton and Butler, 2001), spinal cord injury (Soler *et al.*, 2010) and hemiparesis (Sathian, 2000). Strikingly, the skin regions that induce referred sensations can be mapped to produce a topographical layout of the missing digits (see Figure 4). We initially describe here how somatosensory stimuli are first perceived by the brain in the healthy population, and then outline how the cortex is subsequently altered by amputation so that it produces such referred sensations.

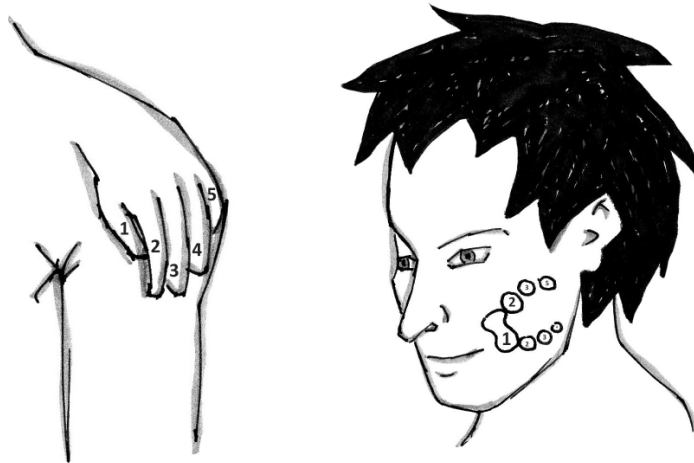


Figure 4: Missing digits are topographically mapped to produce referred sensations from adjacent body parts (adapted from Ramachandran and Hirstein, 1998)

4. 1. The primary somatosensory cortex in the normal-bodied population

4. 1. 1. *The Penfield homunculus*: The reason touch sensations in the phantom hand are referred from the face and stump, and the phantom foot from the genitals and stump, is due to the organisation of the body's representation in the cortex. Somatosensory inputs from the body are projected via the spine to the primary somatosensory cortex located along the post-central gyrus of the parietal lobe. The primary somatosensory cortex in one hemisphere of the brain contains a topographical map of the contralateral side of the body; parts of the body that are physically adjacent in space are represented adjacently in the cortex (Hari *et al.*, 1993; Blankenburg, Ruben, Meyer, Schwiemann and Villringer, 2003). The only few exceptions to this are the close proximity of the face to the hand and the genitals to the foot (Penfield and Boldrey, 1937). According to Farah (1998) this may be due to the foetal position the body is in when this brain region begins to develop in the uterus. The body representation is inverted, with the legs and genitals dorsally located and the face and hands in ventral regions (Hari *et al.*, 1993).

The receptive fields for touch vary in size on different parts of the body (Penfield and Boldrey, 1937; Penfield and Rasmussen, 1950). For example, a smaller area of skin on the fingertips and lips must be stimulated to alter the firing rate of the skin's mechanoreceptors than would be necessary to detect the same stimulus on the calf or back. The smaller the receptive field on the skin, the better the tactile acuity in that region, and thus the larger the

representation of that body part in the primary somatosensory cortex (Weinstein, 1962; Brown, Koerber and Millecchia, 2004). Penfield and Boldrey (1937) introduced the Penfield homunculus as a diagrammatic representation of the areas in the somatosensory cortex with larger representations and more sensitive skin (see Figure 5).



Figure 5: The Penfield homunculus is a visual portrayal of a "little man" in which body parts that are particularly sensitive and have large cortical representations are exaggerated, and less sensitive body parts with smaller representations are underemphasized.

4. 1. 2. *Systematic tactile mislocalisation:* When a part of the body is touched, most healthy human adults have no difficulty ascribing the touch sensation to a particular part of the body. However, errors in reporting the spatial location of the tactile stimulation sometimes occur when the participant is instructed to respond as quickly and accurately as possible (Elithorn, Piercy and Crosskey, 1953; Marshall, 1956), when the view of the limb is obscured (Halnan and Wright, 1960) or when this is done at near-threshold levels (Schweizer, Maier, Braun and Birbaumer, 2000; Schweizer, Braun, Fromm, Wilms and Birbaumer, 2001). These mislocalised sensations do not occur randomly; they emerge in a systematic pattern (Elithorn *et al.*, 1953; Schweizer *et al.*, 2001) and one that reflects the representation of the body in the cortex (Penfield and Boldrey, 1937; Penfield and Rasmussen, 1950).

Touch sensations to a digit of the hand are significantly more often erroneously localised on the digits close to it than on the ones further away from it (Elithorn *et al.*, 1953;

Schweizer *et al.*, 2000; Schweizer *et al.*, 2001; Braun *et al.*, 2005). Thus, Schweizer *et al.* (2001) concluded that even when the participants were unable to detect the touch experience, and were making errors in tactile spatial location, some information about the location had to be unconsciously available, as the errors reflected the organisation in the primary somatosensory cortex. Moreover, they found that systematic tactile mislocalisation could be altered by long-term training. After practice with simultaneous stimulation of a distant and target digit, localisation errors for the target digit shifted towards the distant digit rather than towards the adjacent ones. This type of learning has been associated with plastic topographical change in the primary somatosensory cortex of the normal population as the digit representations merge and lose their normally occurring borders (Clark, Allard, Jenkins and Merzenich, 1988).

4. 2. Neural plasticity and the remapping hypothesis

4. 2. 1. *The neuromatrix*: The concept of neural plasticity goes back at least to the days of Cajal (1894, 1908) and the term was first coined by Minea (1909) in his thesis title which translates from Romanian as "Experimental investigations on morphological variations in sensory neurons (studies of 'plastic reactions')". Neural plasticity, or the plastic brain, refers to the adaptability of an organism, or organ in this case, to change in its environment (Jones, 2000). These, so called, "plastic" changes in the brain are responsible for cognitive development of faculties such as memory, language, learning and perception (Nelson and Bloom, 1997; Stiles, 2000) as well as recovery and rehabilitation after brain damage (Nudo, Plautz and Frost, 2001; Kleim and Jones, 2008). In other words, the changes that are constantly occurring in the brain reflect the changes that consistently present themselves in the environments in which we live. A unique situation therefore presents itself when a part of the body is removed or altered by means of surgery or amputation. The brain must adapt to the physical change of its most immediate environment, i.e. as a consequence of limb loss the primary somatosensory cortex contains a region that no longer corresponds to a body part (Ramachandran and Hirstein, 1998).

Melzack (1990, 1992) was one of the first to propose a modern theory as to how the brain copes with such change to the body and explain the implications of this for phantom limb sensations. The neuromatrix theory proposed that the healthy human brain contains a network of neural systems that generate a pattern of impulses which indicate the body's normal state. Melzack (1992) argued for at least three separate neural circuits that run in parallel: a) the classic sensory pathway that projects via the thalamus to the primary and

secondary somatosensory cortical areas, b) an emotional pathway which sends impulses via the reticular formation of the brain stem to the limbic system, which may be involved in painful or pleasurable phantom sensations, and c) a self-recognition pathway, which ensures the feeling that the body belongs to one's self, and is based mainly in the parietal lobe. According to Melzack (1990, 1992) these systems are congenitally hard-wired in the brain, but are reinforced by means of somatosensory experience. That way when the cortex no longer receives sensory input, the neurosignature continues to provide the amputee with a sense that the limb remains present.

4. 2. 2. *The remapping hypothesis*: Based on preliminary self-reports in humans (Ramachandran *et al.*, 1992a; 1992b) and single-cell recordings in non-human primates (Merzenich *et al.*, 1983a; 1984; Pons *et al.*, 1991), Ramachandran and Hirstein (1998, p. 1613) introduced the "remapping hypothesis" to further explain in detail the neural changes described by Melzack (1990, 1992). As in humans, somatosensory input to the monkey brain is topographically represented along a primary somatosensory strip of cortex in areas 3b and 1 of the parietal lobe (Merzenich, Kaas, Sur and Lin, 1978; Kaas, Nelson, Sur, Lin and Merzenich, 1979). Merzenich *et al.* (1983a; 1983b) transected the median nerve in the hand which was responsible for projecting touch sensations from digits 1-3 to the brain, and used a micro-electrode mapping technique to investigate whether the peripheral denervation would affect the topographical somatosensory homunculus in the adult owl monkey areas 3b and 1. They found that after only three weeks the cortical areas that formerly represented the median nerve reorganised and became reoccupied by the ulnar and radial nerves of the hand, i.e. the input zones that normally border the median nerve input zone expanded their representations into the newly deafferented cortical region. A second study showed that even with greater peripheral nerve damage, as caused by the amputation of a whole digit, the representations of the adjacent digits grew and remapped over a distance of 1-2 millimetres into the previous territory of the missing digit (Merzenich *et al.*, 1984).

Innovative research by Pons *et al.* (1991) received a great deal of attention when they demonstrated that cortical remapping can occur to a much greater magnitude when a larger part of the body has been amputated and for a longer period of time. In the macaque, as in humans, the representation of the upper limb in the cortex is neighboured by the representations of the face and the torso. After amputating the upper limbs of four macaques, Pons *et al.* (1991) found that the 10-14 millimetres long cortical area that normally

represented the missing limb responded to tactile stimulation of the face. Furthermore, this new map of the face was topographically mapped with the chin caudally represented in the area of 3b that bordered with area 1, and the lower jaw represented in rostral parts of 3b neighbouring area 3a (Pons *et al.*, 1991). Studies employing functional magnetic resonance imaging in human amputees have shown that an analogous process occurs in the post-central gyrus of the human parietal cortex (Ramachandran, 1993; Yang *et al.*, 1994a; 1994b; Flor *et al.*, 1995a, 1995b; 1998). Figure 6 portrays the mediolateral invasion of the face and stump representations into the classic hand area of the primary somatosensory cortex. Ramachandran *et al.* (1992a; 1992b; Ramachandran and Hirstein, 1998) hypothesised that it is precisely this cortical remapping by means of neural plasticity in the primary somatosensory cortex that is responsible for referred sensation in human amputees. In other words, the reorganisation that occurs in the brain following amputation means that touch to the stump and face (in upper-limb amputees) or stump and genitals (in lower-limb amputees) would activate the primary somatosensory hand or foot representation, respectively. This would then be interpreted by higher brain regions as touch to the phantom limb.

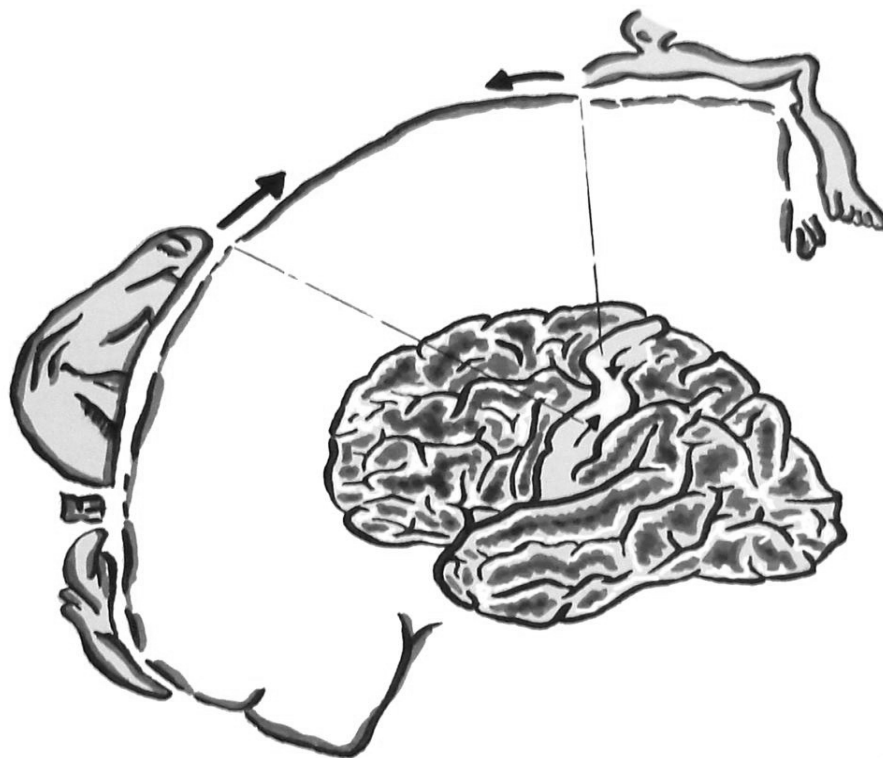


Figure 6: Cortical remapping in the primary somatosensory cortex. After the upper limb has been amputated the brain region that formerly received input from the missing limb is invaded by the expansion of the face and stump representations.

Albeit an attractive explanation for referred sensations in people with phantom limbs, and a process that is generally accepted these days to occur in the brain following limb loss, the perceptual correlates of cortical remapping are still debated. Ramachandran and Hirstein's (1998) hypothesis suggests that neural plasticity and referred sensations are the brain's mechanism for preventing dissonance between the action the cortex aims to execute and the sensation it would expect to receive in response (in accordance with the forward model of motor control; Wolpert and Kawato, 1998; Blakemore, Frith and Wolpert, 1999). Conversely, according to Flor *et al.* (1996) cortical reorganisation in the primary somatosensory cortex is strictly correlated with phantom pain, and non-painful referred sensation are the consequence neural changes in other cortical regions (Flor *et al.*, 1996; Knecht *et al.*, 1996). Flor *et al.* (2000) found that non-painful phantom limb sensations involved an increase in non-shifted primary somatosensory activity and posterior parietal activity as well as a decrease in the activity of the secondary somatosensory cortex. Despite the increased activation in the primary somatosensory cortex for these non-painful sensations, invasion of the neighbouring areas into the previous hand area was only found for nociceptive stimuli. The regions described by Flor *et al.* (2000) fall in line with parts of the brain that earlier research suggested were involved in the neuromatrix and perception of general phantom limb sensations (Pons, Friedman, Garraghty, O'Neill and Mishkin, 1986; Melzack, 1990, 1992; Jones and Pons, 1998). Moreover, Davis *et al.* (1998) showed that the thalamus, also implicated by the neuromatrix, is involved in the perception of referred sensations by human amputees.

4. 2. 3. *Sprouting versus unmasking*: Another historical dispute in this field lies in explaining exactly what physiological mechanism drives plasticity and cortical remapping. One possibility is that when a region of the primary somatosensory cortex is silenced due to the loss of afferent input, the neurons in the adjacent cortical regions physically sprout new dendrites, extend their axons and form new synaptic connections with neurons in the neighbouring regions (Hoffman, 1952; Woolf, Shortland and Coggeshall, 1992). However, a classic argument against synaptogenesis when it comes to explaining neural plasticity after amputation is that the process is a time consuming one, and phantom limb sensations are normally perceived as soon as the patient becomes conscious after amputation (Borsook *et al.*, 1998).

Wall (1977) alternatively proposed that pre-existing, but ineffective, synaptic connections between neurons representing different body parts become unmasked when the

peripheral excitatory input is removed. Support and expansion of this theory comes from studies such as Rasmusson and Turnbull (1983) who amputated a single digit in nine raccoons and recorded the electrical activity in the cortical region known to respond to that digit. The authors found that as soon as two hours after amputation, these cells responded to tapping on the adjacent digits. This response, however, was inhibitory in nature. Recording from the same cortical area 8-20 weeks later led to the conclusion that inhibitory responses are unmasked immediately after amputation, and with time these are replaced by excitatory impulses (Rasmusson and Turnbull, 1983). As the time course is so rapid it seems that the mechanism involved here is the unmasking of previously existing inhibitory connections in the primary somatosensory cortex.

Ironically, however, a recent study reached similar conclusions about an immediate inhibitory response followed by an excitatory one by imaging the cortical neurons of mice labelled with a genetically modified virus. They, conversely, show that sprouting does indeed occur after sensory deprivation and soon after the peripheral damage (Marik, Yamahachi, McManus, Szabo and Gilbert, 2010). After plucking the whiskers of adult mice, Marik *et al.* (2010) showed that inhibitory neurons from the deafferented cortex extended their axons into the adjacent cortical regions; excitatory axons from neurons in these areas subsequently invaded the deafferented cortex at a slightly more gradual pace. The role of the inhibitory neurons in this case may be to maintain the balance between the excitation and inhibition in line with the rest of the cortex, hence mirroring their role in post-natal development (Marik *et al.*, 2010).

For a while the generally accepted conclusion to this debate was that rapid changes in sensory perception were due to unmasking of pre-existing synapses involving modulation of inhibition, and that sensory changes that occur over a longer period of time involved additional mechanisms such as axonal regeneration and dendrite sprouting (Chen, Cohen and Hallett, 2002, Pascual-Leone *et al.*, 2005). Nevertheless novel neuroimaging and molecular techniques emerging at present are beginning to suggest that neurogenesis occurs at a greater rate than was previously presumed, and that the brain may show even greater levels of plasticity than was originally thought (Fu and Zuo, 2011). As this field is constantly developing it is still unclear what the precise implications are for phantom limb sensations and pain. It is vital that researchers in the field of amputation follow this closely.

4. 3. Relating to the current research

Regardless of the mechanisms driving the phenomenon and the associated perceptual experiences, the purpose of cortical remapping in amputees remains unclear. Early research seemed to indicate that limb loss enhances tactile spatial acuity on the stump (Katz, 1920; Teuber, Krieger and Bender, 1949; Haber, 1955, 1958; Wilson *et al.*, 1962), thus suggesting a functionally adaptive reason for such reorganisation. However, later studies have failed to replicate these findings (Braune and Schady, 1993; Moore and Schady, 2000; Vega-Bermudez and Johnson, 2002) or show a link between tactile sensitivity and neural plasticity (Flor *et al.*, 1998; Grusser *et al.*, 2001). Paper 4 attempts to resolve this issue by measuring the cutaneous sensitivity of the facial skin in upper-limb amputees. The paper also directly compares the tactile acuity of individuals with acquired amputation to those with congenital limb deficiency. The fifth, and final, paper in this thesis proposes a possible methodology for empirically testing referred sensations. To date all studies demonstrating referred sensations in amputees rely on self-reports or correlational neuroimaging techniques. Ehrsson *et al.* (2008) demonstrated the presence of referred sensation in amputees by manipulating the rubber hand illusion, but this was limited to sensations referred from the sensitive stump skin only. In Paper 5 we test for referred sensations by adapting the selective attention paradigm of orthogonal cuing introduced by Driver and Spence (1998a, 1998b) for upper-limb amputees.

5. General Discussion

This thesis sets out to explore the perceptual experiences of amputees and discover how they differed from those of the normal-bodied population. Our research focused specifically on painful, visual and tactile perceptions and examined the cross-sensory interactions between these. In line with much research in this field, the first paper found no difference in frequency or intensity of phantom limb pain based on the physical characteristics of the amputation or the non-painful perceptual phenomena associated with the phantom (Jensen *et al.*, 1983; Sherman and Sherman, 1983; Jensen *et al.*, 1985; Sherman and Sherman, 1985; Kooijman *et al.*, 2000; Davidson *et al.*, 2010). However, we did identify differences between amputees whose phantom pain was trigger-induced and amputees whose pain seemed to occur at random. Namely, amputees with trigger-induced pain (e.g. from rest, exercise, verbal reference, etc.) also experienced higher intensities of phantom pain and their general phantom sensations occurred more frequently than amputees with randomly

occurring pain. This group also consisted of a significantly larger percentage of upper-limb amputees relative to those with lower-limb amputations.

The subsequent two papers in the thesis investigated the interactions between vision and motor sensation by taking a closer look into possible mirror system related behaviours in perception for action. Paper 2 was the first in the field to perform a large-scale study into the detailed characteristics of acquired mirror-touch synaesthesia and those who are likely to experience it. The results showed that like developmental mirror-touch synaesthetes (Banissy and Ward, 2007), amputees with mirror-touch sensations had higher emotional reactivity EQ scores than those without mirror-touch synaesthesia. But unlike in developmental synaesthesia (Holle, Banissy, Wright, Bowling and Ward, 2011), somatotopy is not preserved in mirror-touch amputees; regardless of where the observed touch is located, its concurrent touch sensation is perceived to occur in the phantom limb. Similar nonsomatotopic synaesthetic referrals have been observed after other forms of sensory loss (Evans, 1976; Ro *et al.*, 2007), indicating perhaps a difference between acquired and developmental synaesthesia.

In the third paper the workings of the mirror system in amputees was also examined, but the concentration in Paper 3 was on the more subtle perceptual effects that occur at sub-threshold levels of consciousness. It was hypothesised that if observing and executing an action relied on the same system, then interpretation of an observed action may be impaired by the inability to perform such an action. However, when it came to the perception of apparent biological motion, amputees showed a similar, albeit dampened, pattern of results to normal-bodied controls (Shiffrar and Freyd, 1990, 1993). This would suggest that although losing a limb may alter perception to an extent, persistent phantom limb sensations remain the best indication of a functional body schema (Funk *et al.*, 2005). Such phantom sensations may arise from the conflict between an online representation which informs the body schema that action cannot be carried out without the missing limb, and an offline representation that fails to update the body schema that the constant state of the body has changed (Gallagher and Cole, 1995; Carruthers, 2008; Berlucchi and Aglioti, 2010). It is perhaps the maintained offline body schema that caused the amputees to perceive a similar pattern of biological motion as the control participants.

The final two papers concentrated on perceptual phenomena linked with the neural plasticity after amputation, namely tactile acuity and referred sensations. Paper 4 was concerned with the functional purpose of cortical remapping associated with amputation. In this paper we made a novel contribution to phantom limb research by testing for differences in

tactile acuity on the two sides of the face, and directly comparing the cutaneous sensitivity of those with acquired versus congenital limb loss. Despite controlling for the confounding variables of previous studies, our findings followed along similar lines to previous research (Braune and Schady, 1993; Moore and Schady, 2000; Vega-Bermudez and Johnson, 2002; Hunter, Katz and Davis, 2005, 2008); there was no difference in the tactile acuity between the face areas ipsilateral and contralateral to the amputation site, or between amputees, congenital cases and normal-bodied controls. Vega-Bermudez and Johnson (2002) suggested that this could be because the primary somatosensory cortex maintains its original function or because the brain regions responsible for tactile acuity are not in fact located in the primary somatosensory cortex. Of interest, though, is that across all participant groups we found that the side of the face ipsilateral to the non-dominant hand in controls, and the non-existent hand in the clinical populations, displayed significantly higher tactile acuity than the side of the face ipsilateral to the dominant, or intact, hand (see also Lee and Essick, 1993). This could be because the dominant hand's topographical representation in the primary somatosensory cortex is genetically larger (White, Lucas, Richards and Purves, 1994; Beaton, 1997; Corballis, 2009), which might shrink the adjacent representation of the face causing it to show lower tactile acuity in all participants.

To further enhance our understanding of neural plasticity, the final chapter emphasised the importance of finding a standardised empirical method for measuring referred sensations. We set out to do this by employing the orthogonal cuing paradigm for selective attention (Driver and Spence, 1998a, 1998b), but found the cuing effect to be so strong that it overshadowed the sensations; not only did referred sensations not have an impact on spatial discrimination decisions, but also the physical location of the tactile stimuli meant to elicit the sensations did. Despite not successfully introducing a systematic methodology for measuring referred tactile sensations, we hope that by drawing attention to this issue we have highlighted the importance of doing so. Future research in this field should perhaps follow suit with Ehrsson *et al.* (2008) and focus on the rubber hand illusion (Botvinick and Cohen, 1998). If the referred sensations from the face and stump are qualitatively similar, it can be assumed that stroking the face and rubber hand congruently would cause the phantom to be perceived as closer in space to the rubber hand.

Although our findings are generally correlational, as we did not directly compare the perceptual experiences of the same participants before and after amputation, taken together they permit us to draw conclusions with regards to abnormalities in amputees relative to the normal-bodied population. It could be argued that the mere illusion of possessing a limb that

is not physically present is not perceptually normal. Furthermore, experiencing pain in external physical space that is outside of the body's limits is not a regular occurrence in the general population. In the current research we demonstrated that phantom limb perception goes beyond pain; some amputees also felt referred tactile sensations in the phantom limb when they were touched on adjacent parts of the body or when they observed another person's body being touched. In contrast, some perceptual systems appeared to resist the effects of amputation. For example, the tactile sensitivity of the amputees' faces were similar to those of both the congenital cases and control participants, and their perception of apparent biological motion was about normal.

On the whole, our findings seemed to indicate that the body schemas, mirror-systems and pain matrices of amputees who experienced phantom sensations were only moderately affected by the physical change to the body. However, in some amputees these systems and mental representations appeared to enhance beyond their normal sub-threshold levels into consciousness. It is essential that future work in the fields of psychology, neuroscience and neurology research not only look at the individual differences that make these amputees unique, but also design studies to uncover the structural and chemical neural changes that may lead to this. Interesting comparisons could be drawn with people whose online body representation was normal, but who had an impaired offline representation, such as those with body integrity identity disorder (Hilti and Brugger, 2010), or with people whose online and offline representations were impaired, such as is seen in patients with eating disorders (Urgesi *et al.*, 2011; Mohr *et al.*, 2010). These kinds of disorders are often only investigated in their social or psychiatric contexts, but more and more research these days is looking into the *perceptual* anomalies of these populations.

Due to the rise in life expectancy and development of medical and prosthetic technology people are living longer and are more likely to survive an amputation than ever before. In modern times amputation as a consequence of war injuries (Robbins, Vreeman, Sothmann, Wilson and Oldridge, 2009) and chronic diseases (Dillingham, Pezzin and MacKenzie, 2002) is constantly increasing, and research into aiding sufferers is as important as ever. A recent study showed that 1.6 million people living in the United States had endured an amputation by 2005, and based on their age, sex, race and aetiology this number was projected to more than double by 2050 (Ziegler-Graham, MacKenzie, Ephraim, Trivison and Brookmeyer, 2008). By examining the perceptual experiences of amputees, this thesis aimed to provide further insight into the experiences of amputees and contribute to the pool of knowledge in this field. Exploring the behavioural and cognitive correlates of phantom pain

enables medical professionals to develop treatments and cures for such disabling experiences. However, when studying perception in amputees, it is imperative that further research not only focus on phantom pain and acquired amputation. Studying other phenomena, such as referred sensations and mirror-touch synaesthesia, and other patient groups, such as those with congenital phantoms, is also vital in order to broaden our understanding of phantom limb phenomena and enhance technology in the development of prosthetic limbs and other aids for disability.

Paper 1

The epidemiology of phantom limb pain: The role of physical amputation characteristics and non-painful phantom limb phenomena

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Phantom pain in the absent limb is often described after amputation. Yet, the precise causes and perceptual correlates of this pain seem to vary from sample to sample. In this study 106 people with at least one missing limb were recruited through a prosthetic limb fitting centre of the National Health Service. In sections of a structured questionnaire participants were asked about 1) phantom pain frequency, intensity and inducers, 2) physical/medical factors about the amputation, and 3) non-painful phantom limb phenomena. A second questionnaire addressing phantom pain in more detail was completed by 54 of the participants two years later. Amputees whose pain was trigger-induced (e.g. as a result of rest or stress) were found to experience phantom limb pain significantly more often than those whose pain seemed to occur at random. Phantom pain was also more intense, and sensations more frequent, in amputees where the site of amputation was above the joint. The data revealed a trend (albeit not a statistically significant one) of higher levels of phantom pain in those who experienced more pain prior to amputation. No differences were found in phantom pain based on sex, time since amputation, limb amputated, cause of amputation, dominance of missing limb, presence of synaesthesia, telescoping, prosthesis use and its embodiment, or phantom mobility. We conclude that to learn more about effects of the proximity of the limb to the torso it would be wise to investigate the relationships between level of amputation, prosthesis use, telescoping and pain. This study also emphasised the importance of further investigating what triggers phantom pain in amputees and why those with such trigger undergo stronger pain sensations.

1. Introduction

Neural plasticity, a term referring to the constant changes that occur in the central nervous system, is an adaptive trait that allows the brain to accommodate learning, develop specific skills and fine-tuned kinaesthetic actions. However, in the case of cortical changes associated with limb amputation, this plasticity has been linked to chronic pain in the resulting phantom limb (Flor *et al.*, 1995; Lotze, Flor, Grodd, Larbig and Birbaumer, 2001). The precise prevalence of general phantom limb sensations and phantom limb pain often depends on the sample selected or method of measurement. However, it is generally agreed that nearly all amputees experience some form of phantom limb sensation at some point after their amputation (70-100% Wartan, Hamann, Wedley and McColl, 1997; Richardson, Glenn, Nurmikko and Horgan, 2006; Giummarra *et al.*, 2010), and that for most of these there is some level of pain associated with the phantom limb (50-80% Steinbach, Nadvorna and Arazi, 1982; Jensen, Krebs, Nielsen and Rasmussen, 1983, 1985; Houghton, Nicholls, Houghton, Saadah and McColl, 1994). Prevalence of phantom sensations in those with congenitally missing or malformed limbs is much lower (4-20% Melzack, Israel, Lacroix and Schultz, 1997; Wilkins, McGrath, Finley and Katz, 1998; Kooijman, Dijkstra, Geertzen, Elzinga and van der Schans, 2000), perhaps because of absence of amputation-related neural plasticity in this population. Non-painful phantom sensations are normally more common than painful ones (e.g. Smith *et al.*, 1999), but amputees with non-painful phantom sensations are more likely to also have phantom pain (Wartan *et al.*, 1997).

Theories to explain phantom limb pain vary from the emergence of repressed pre-amputation memories (Katz and Melzack, 1990) to the hypersensitivity of neuromata in the residual stump (Wall and Gutnick, 1974), and from unconscious amputation bereavement and wish-fulfilment (Zuk, 1956) to a matrix of neural networks that form a central neurosignature for pain (Melzack, 1990, 1992). Whilst one school of thought holds that cortical reorganisation in the primary somatosensory cortex is directly responsible for chronic pain in the phantom limb (Grusser *et al.*, 2001; Lotze *et al.*, 2001; Flor, 2002; Flor, Nikolajsen and Jensen, 2006), another holds that this very reorganisation has evolved to prevent phantom limb pain after amputation (Ramachandran, Stewart and Rogers-Ramachandran, 1992; Yang *et al.*, 1994; Ramachandran and Hirstein, 1998). What are less commonly researched are the individual differences between amputees in terms of the quality, intensity and frequency in phantom limb pain and what it is that leads to these differences. For example, Wartan *et al.* (1997) found that 34% of their sample had constant or daily experiences of phantom pain, but 41%

had only a few attacks of pain per month; and the intensity of such phantom pain at its worst tends to vary within and amongst amputees (Wartan *et al.*, 1997; Richardson *et al.*, 2006).

Research has investigated the role of pre-operative pain intensity and duration in determining the differences between amputees in quality of later phantom pain (Jensen *et al.*, 1983, 1985; Katz and Melzack, 1990; Nikolajsen, Ilkjaer, Kroner, Christensen and Jensen, 1997; Davidson, Khor and Jones, 2010), and results have been divided. It seems that pre-operative pain correlated with the phantom limb pain experienced one week, three months and six months following amputation (Jensen *et al.*, 1983, 1985; Nikolajsen *et al.*, 1997), but that after a period of two years there is no difference in levels of phantom pain between those who experienced pain in the limb prior to amputation and those who did not (Jensen *et al.*, 1985). Katz and Melzack (1990) found that in 57% of their cases phantom pain was qualitatively similar to pre-operative pain, but other studies found no relationship between the pain experienced previous to limb-loss and that in the phantom limb (Wartan *et al.*, 1997; Kooijman *et al.*, 2000; Davidson *et al.*, 2010).

The period of time that has passed since the amputation has also been looked at to establish whether phantom pain changes as time progresses, and whether this may be why some amputees report experiencing more pain than others do (Jensen *et al.*, 1983, 1985; Houghton *et al.*, 1994; Flor *et al.*, 1995; Wartan *et al.*, 1997; Richardson *et al.*, 2006; Giummarra *et al.*, 2010). Some studies have shown a decrease in visual analogue scores over a period of six months to five years (Houghton *et al.*, 1994; Richardson *et al.*, 2006), or a decrease in the frequency of phantom pain amongst amputees over a period of two years (Jensen *et al.*, 1985), but others found no relationship between the time that had passed since the amputation and the quantity of phantom pain (Sherman, Sherman and Parker, 1984; Flor *et al.*, 1995; Montoya *et al.*, 1997; Wartan *et al.*, 1997; Giummarra *et al.*, 2010). Similarly no differences have been reported in the age at which amputation occurred between those with phantom limb pain and those without it (Sherman *et al.*, 1984; Wartan *et al.*, 1997; Kooijman *et al.*, 2000).

The final main focus in the literature on the predictors of phantom pain has been on the details of the amputation and the physiological differences between the amputees. The incidence of phantom pain in upper-limb amputees has been reported to be significantly higher than its incidence in lower-limb amputees, and higher levels of phantom pain have been associated with amputation of the dominant limb (Shukla, Sahu, Tripathi and Gupta, 1982). One study found a difference between males and females, where women reported more

intense phantom pain (Weiss and Lindell, 1996). Despite finding that vascular amputees experienced significantly more pain prior to amputation than traumatic amputees, Houghton *et al.* (1994) found that there was no difference between these two groups in their amount of phantom limb pain. Other studies have also found no differences in the percentages of amputees who experienced phantom pain based on whether it was the dominant limb that was amputated, the proximity of the amputation to the torso, prosthesis use, prosthesis type, gender, number of amputations or reason for amputation (Sherman *et al.*, 1984; Wartan *et al.*, 1997; Kooijman *et al.*, 2000).

An area often neglected is the influence of other amputation-linked phenomena on the frequency and intensity of phantom limb pain. As a recent epidemiological study pointed out, many authors have reported the perception of somatic non-painful phantom phenomena, but not many have systematically investigated these (Giummarra *et al.*, 2010). In an attempt to rectify this, Giummarra *et al.* (2010) provided an intensive overview of corporeal and proprioceptive phantom limb qualities, namely the physical nature of the phantom's posture and size, "external" sensations involving touch and temperature, and the ability of the limb to embody a prosthesis. Telescoping refers to the change in size or length of the phantom limb, typically shrinking, and is reported in 22-36% of amputees (Fraser, 2002; Giummarra *et al.*, 2010). This phenomenon has been hypothesised to evolve as a means to prevent phantom limb pain (Katz, 1992). Giummarra *et al.* (2010) reported that up to 20% felt that their phantom limb embodied the prosthesis when it was worn, and that this was more frequent in non-telescoped limbs. One study has reported a decrease in phantom pain when using a functional, rather than cosmetic, prosthesis (Weiss, Miltner, Adler, Bruckner and Taub, 1999), but otherwise no difference in phantom pain has been reported based on duration of prosthesis use (Wartan *et al.*, 1997), embodiment (Giummarra *et al.*, 2010) or telescoping (Montoya *et al.*, 1997; Richardson *et al.*, 2006). Other phantom experiences include synaesthetic mirror-touch sensations when observing touch or movement (Ramachandran and Brang, 2009; Fitzgibbon *et al.*, 2010a; Fitzgibbon, Giummarra, Georgiou-Karistianis, Enticott and Bradshaw, 2010b) and the ability to move the phantom limb by choice or spontaneously (Richardson *et al.*, 2006), but little has been reported on the relationship between these and phantom limb pain.

The aim of the current study is to develop a novel questionnaire to gain insight into phantom limb pain in a new population of people who have experienced limb-loss due to amputation or congenital abnormalities. The relationship between the frequency and intensity of phantom pain and pre-operative pain, time since amputation and physiological

attributes are reexamined. Moreover, differences in phantom pain are investigated between those who experience other phantom phenomena, such as mirror-touch synaesthesia, telescoping and mobility. This research also looks at the epidemiology of phantom pain inducers. Certain factors, such as the weather change, prosthesis malfunction, mental stress and fatigue have been reported to intensify or induce episodes of phantom limb pain in some amputees (Sherman *et al.*, 1984; Giummarra and Bradshaw, 2011). It is unclear whether the intensity or frequency of phantom pain in these amputees is different from that in amputees who do not report reliable triggers. This questionnaire was designed in order to enhance the scientific pool of knowledge with regards to the painful and non-painful consequences of amputation.

2. Method

2. 1. Participants

Of the questionnaire respondents 95 had acquired an amputation, whilst 11 were born with malformed or missing limbs and had not undergone any corrective surgery. The amputees (69 male, 26 female) ranged in age from 19 to 91 years (Mean = 57.48, SD = 15.39). The average age at amputation was 38.25 years (SD = 20.92, range = 2-87) and an average of 20.02 years (SD = 7.90, range = 1-76) had elapsed between undergoing the amputation and completing the questionnaire. A subset of amputees (N = 54) also completed a follow-up questionnaire approximately two years later. The questionnaires were sponsored by the Life Sciences Ethics Committee at the University of Sussex and approved by the Brighton East Research Ethics Committee of the National Health Service (see Appendix A).

The congenital cases (4 male, 7 female) ranged in age from 25 to 64 years (Mean = 47.66, SD = 15.76). The congenital participants were not included in the data analysis as only three of them experienced any form of phantom sensations, and none had ever experienced phantom pain.

2. 2. Materials

Based on the phantom limb literature, a questionnaire entitled "Limb Deficiency and Phantom Limb Questionnaire" was devised to assess the participants' physiological and

surgical history, details of the pain and limb sensations prior to and immediately after amputation, phantom limb sensations and subjective thoughts, feelings and sensations (see Appendix B). Based on the outcome of the original questionnaire and follow-up interviews, a second questionnaire titled "Phantom Pain Questionnaire" was developed to further address details about the cause of amputation, reasons for multiple operations, quality of the pain before, phantom pain after amputation and empathy quotient of amputees (see Appendix C). The following questions were used here for the analyses addressing phantom pain.

2. 2. 1. Phantom limb pain frequency, intensity and inducers: The key dependent variables throughout all analyses were the frequency of general phantom limb sensation, the frequency of phantom limb pain and the intensity of phantom limb pain. The frequency questions asked how often the phantom experience (sensations or pain) occurred and answers were provided by selecting an option coded on a scale of 1-8: 1) Less than once a month, 2) Once a month, 3) Once a fortnight, 4) Once a week, 5) Several times a week, 6) Once a day, 7) Several times a day, and 8) Permanent. Phantom pain intensity was indicated by putting a straight line through a 100 millimetre visual analogue scale labelled with "No Pain" at one extreme and "Unbearable Pain" at the other, when asked about the level of pain associated with the phantom limb at its worst. The intensity of the pain in the limb immediately prior to amputation was measured in the same way. The duration of the pain prior to amputation was indicated on a scale of 1-6: 1) A few hours, 2) Several days, 3) One week, 4) One month, 5) Several months, and 6) More than six months. Participants provided their date of birth and age at amputation in their personal information, and these were used to compute the number of years that had passed since the amputation.

The original questionnaire asked the open question, "Is this pain associated with any events in daily life (e.g. stress, rest, exercise)?" The answers were coded as dichotomous "Yes" or "No" responses. Based on their detailed responses a follow-up questionnaire later asked if any of the following triggered painful phantom limb sensations: Rest (e.g. watching television), Bedtime or sleep, Strenuous activity (e.g. exercise), Stress, Verbal reference to amputation/phantom and Seeing someone in pain. Participants were asked to indicate all that apply and were given space to detail any other triggers of phantom limb pain.

2. 2. 2. Physical/medical factors in phantom limb pain: Participants were presented with a line drawing of the human body which was labelled for laterality, and were asked to indicate the location of amputation and its distance in centimetres or inches from the elbow or knee (see example in Figure 1). Number of amputation sites (unilateral, bilateral or multiple-limbs), type of amputation (upper- versus lower-limb) and level of amputation (above- versus below-joint) were inferred. In the participant personal information box on the front of the questionnaire participants provided their sex and hand/foot dominance prior to amputation.

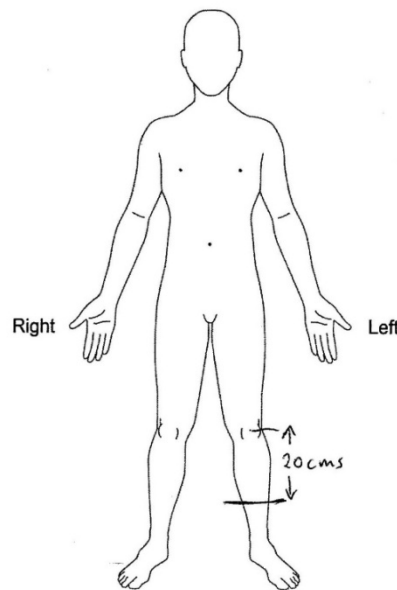


Figure 1: Example of markings by a left unilateral below-knee lower-limb amputee.

An open-ended question asked participants to describe the reasons for their limb deficiency. Examples such as "Congenital due to..." and "Amputation resulting from..." were provided. Responses were grouped based on their acquired versus congenital origin, and the acquired amputations were further coded based on their cause: Traumatic injury, Vascular disease (including diabetes), Infection (including MRSA), Cancer and Birth defect.

2. 2. 3. Differences in phantom pain based on non-painful phantom limb phenomena: A series of dichotomous "Yes" or "No" questions investigating phantom limb mirror-touch sensations, telescoping, prosthesis use and embodiment and mobility were presented on the penultimate page of the questionnaire. There were four questions to address mirror-touch

synaesthesia with regards to experiences in the phantom limb when: 1) seeing someone else move their equivalent limb, 2) seeing someone else being touched, 3) seeing another person in pain, and 4) when the intact limb is experiencing sensations or carrying out actions. Three questions about mobility asked if: 1) the participants could move their phantom limb by choice (e.g. to wiggle the fingers or toes), 2) the phantom moved spontaneously (e.g. to avoid being hurt or to instinctively grab hold), and 3) it felt like participants had the ability to carry out combined movements of the intact and phantom limb (e.g. gesticulating). To measure prosthesis use and embodiment the questionnaire first asked whether the participant had ever used a prosthesis, then if they still use it and finally if when wearing the prosthetic limb they felt as though the phantom limb occupied the same space as the prosthesis. Two questions on telescoping looked into whether the phantom hand/foot size appear to be normal, enlarged or shrunk, and whether the arm/leg length appeared to be normal, longer or shorter.

2. 3. Design and Procedure

From a database of registered prosthetic limb users at the Sussex Rehabilitation Centre in Brighton, a quasi-random sample of 380 patients were posted letters of invitation, information sheets, questionnaires and consent forms of which 106 valid questionnaires and consent forms were returned. Selection of participants targeted primarily upper-limb amputees and those caused by traumatic injury, with a preference for younger ages, so as not to confound results by cognitive impairment associated with old age and illness. Questionnaires were posted in June 2008 by the Sussex Rehabilitation Centre. The Data Protection Act 1998 was not violated as we only had contact with the patients if they chose to respond and provide us with their details. The letter of invitation clearly stated that "[i]f you decide not to take part in this research then you don't have to do anything". The Sussex Rehabilitation Centre was not informed of which patients chose to take part in the research so that their treatment could not be affected. In March 2010 a follow-up questionnaire was sent by post to any of the amputees who had provided us with their address details in the first questionnaire. A total of 54 were returned.

2. 4. Statistical Analyses

Student's t-tests were used to compare the means of two groups when interval or ratio data were available and normally distributed, such as phantom pain intensity. Degrees of

freedom were adjusted on occasions where the homogeneity of variance assumption was not met. When only ordinal data were available, like frequency of phantom sensations and phantom pain, Mann-Whitney U tests were used to compare means, and Spearman's rank correlations were conducted when testing for relationships between variables. For parametric correlations, e.g. time since amputation and phantom pain intensity, a Pearson's test was used. Univariate chi-Squared tests were employed to compare frequency data with dichotomous variables; for example to compare the number of lower-limb amputees with trigger-specific pain to the number of upper-limb amputees with trigger-specific pain. Analyses were theory-driven. Differences and correlations were considered significant when two-tailed probabilities were equal to or less than .05.

3. Results

3. 1. Phantom limb pain frequency, intensity and inducers

Of the 95 amputees, 94.74% reported feeling some form of phantom limb sensation, and of these 88.89% scored phantom pain intensity as at least 5/100 indicating that they experienced some form of phantom pain. Non-painful phantom limb sensations were reported by 71.20% of the sample to either persist permanently ($n = 25$) or to occur at least several times a week ($n = 37$), whilst the frequency of painful phantom limb experiences was more dichotomous; 43.80% experienced phantom pain multiple times during the day ($n = 23$) or permanently ($n = 9$), but 16.40% only experienced such pain less than once every six months ($n = 12$). On a scale ranging from 0 (no pain) to 100 (unbearable pain) the mean phantom pain intensity was 45.96 ($SD = 33.22$, $N = 91$) across all the amputees in the sample. Phantom pain intensity and phantom pain frequency did not correlate with each other ($r_s = .194$, $p = .104$, $N = 71$). The frequency of overall phantom sensations also did not correlate with phantom pain intensity ($r_s = -.006$, $p = .954$, $N = 85$), but it did positively correlate with the frequency at which phantom pain was experienced ($r_s = .373$, $p = .001$, $N = 70$), i.e. the more frequently amputees experienced general phantom limb sensations the more frequently they experienced pain in that phantom.

The intensity of the pain experienced prior to amputation ($M = 47.30$, $SD = 42.18$) was not statistically different to the phantom limb pain intensity ($t_{(87)} = .251$, $p = .803$). For 63.50% of the sample pain persisted for several months ($n = 18$) and sometimes even more than six months ($n = 22$) before the limb was amputated. However, neither the intensity of the pain

experienced prior to amputation nor the period of time that this pre-amputation pain persisted significantly correlated with the intensity ($r = .186$, $p = .083$, $N = 88$ and $r_s = .043$, $p = .738$, $N = 62$, respectively) or frequency ($r_s = -.003$, $p = .977$, $N = 73$ and $r_s = -.110$, $p = .437$, $N = 52$, respectively) of phantom limb pain.

Based on the self-reported questionnaire responses there was no significant correlation between phantom pain intensity or phantom pain frequency and the amount of time that had elapsed since the amputation ($r = -.091$, $p = .399$, $N = 88$ and $r_s = -.205$, $p = .082$, $N = 73$, respectively). However, although not statistically significant ($t_{(51)} = 1.698$, $p = .096$), phantom pain intensity scores decreased when comparing participants' original data in 2008 ($M = 54.10$, $SD = 34.95$) to their scores in response to the same question in 2010 ($M = 48.00$, $SD = 31.82$). Despite the decrease in phantom pain overall, there was significant positive correlation between phantom pain intensity reported in 2008 and that reported in 2010 ($r = .703$, $p < .001$, $N = 52$; see Figure 2), indicating that reports of phantom limb intensity are consistent over a long period of time.

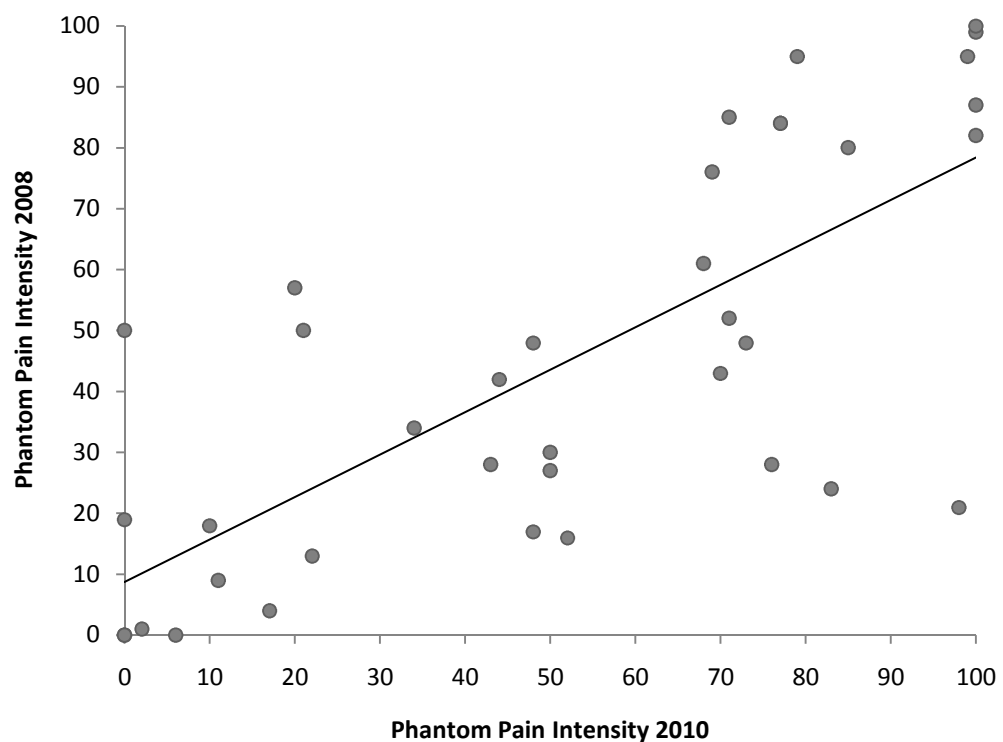


Figure 2: Positive correlation between the intensity of phantom limb pain reported in 2008 and that reported in 2010.

Those amputees who reported an association between phantom pain and certain daily life events (e.g. stress, rest or exercise; 45.70% of the sample) experienced significantly more intense phantom limb pain ($M = 60.31$, $SD = 30.36$) than those whose phantom pain was not associated with particular triggers ($M = 44.44$, $SD = 30.81$; $t_{(77)} = 2.294$, $p = .024$). These trigger-specific amputees did not, however, experience phantom limb pain or general phantom limb sensations more frequently than those who didn't ($U = 529.500$, $z = -1.170$, $p = .242$, and $U = 552.500$, $z = -1.910$, $p = .056$, respectively).

Bedtime or sleep, periods of rest (e.g. watching television) and strenuous activity (e.g. exercise) were the most common triggers of phantom limb pain (see Figure 3) with a third to half of the participants reporting these as pain-inducers. There was no significant difference in phantom pain intensity based on whether or not any of these particular incidents acted as triggers (all $p > .05$). Verbal reference to amputation or the phantom limb was reported to cause phantom pain sensations by 18.50% of the amputees, and 14.80% of respondents claimed that stress triggered phantom pain. Only 4/54 amputees found a relationship between seeing someone else in pain and phantom limb pain. Other causes of phantom pain included stump irritation, weather changes, listening to music, taking medication and expressed concern by others; each of these was reported by only 1-2 participants.

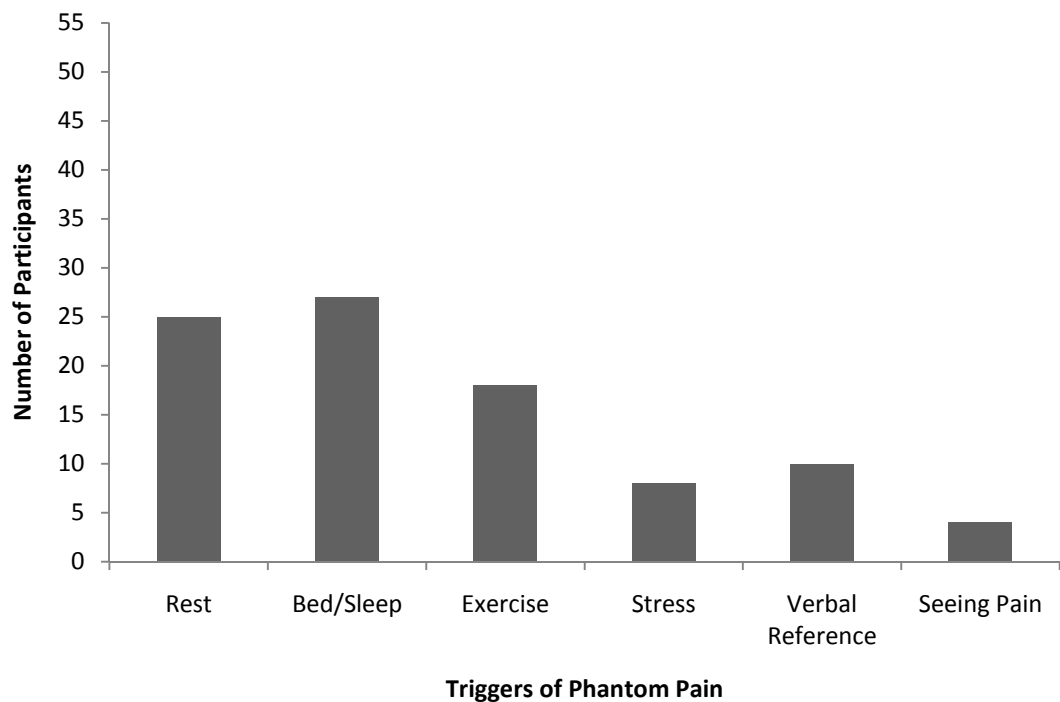


Figure 3: Number of participants out of 54 who reported specific triggers of phantom limb pain.

3. 2. Physical/medical amputation factors in phantom limb pain

No significant difference was found between upper- and lower-limb amputees in phantom pain intensity ($t_{(88)} = 1.220$, $p = .226$) or phantom pain frequency ($U = 221.000$, $z = -1.148$, $p = .251$). However, seven of the nine upper-limb amputees (77.78%) reported an association between certain triggers and phantom limb pain, whereas a significantly lower percentage of lower-limb amputees reported such an association (42.25%; $\chi^2_{(1)} = 4.055$, $p = .044$). Level of amputation played a larger role in phantom limb pain, as above joint amputations brought about more intense pain ($M = 58.83$, $SD = 31.90$) than distal below joint amputations ($M = 37.37$, $SD = 32.37$; $t_{(81)} = 2.894$, $p = .005$). Those with proximal amputations also experienced general phantom sensations ($Mdn = 7$, $IQR = 7-8$) more frequently than those with distal amputations ($Mdn = 5$, $IQR = 3-7$; $U = 420.000$, $z = -2.977$, $p = .003$), but there was only a borderline difference between the two groups in frequency of phantom limb pain ($U = 377.500$, $z = -1.948$, $p = .051$). The dominant limb had been amputated in 50.80% of lower-limb amputees and in 80.00% in upper-limb amputees; across these groups no difference was found between whether it was the dominant or non-dominant limb to be amputated and phantom pain intensity ($t_{(63)} = 1.293$, $p = .201$), phantom pain frequency ($U = 362.000$, $z = -.104$, $p = .917$) or the frequency of general phantom limb sensations ($U = 455.000$, $z = -.537$, $p = .591$). There was also no significant difference between males and females in phantom pain intensity ($t_{(89)} = .810$, $p = .420$) or frequency ($U = 567.500$, $z = -.091$, $p = .982$).

The pie chart in Figure 4 shows the frequency of the various causes of amputation in the sample. All amputations caused by vascular disease, infection and cancer resulted in the experience of phantom limb sensations, whilst one participant who underwent an amputation because of a deficiency at birth and three amputees whose amputations resulted from traumatic injuries did not experience any phantom limb sensations. Of those with a congenitally missing limb only 27% experienced any phantom limb sensations. For the purpose of analysis, vascular disease, infection and cancer were grouped as long-term causes of amputation (shades of blue in Figure 4) and compared to traumatic injury which was considered as a sudden cause of amputation. Congenital cases and those born with limb deficiencies were excluded due to their small sample sizes and lack of phantom limb sensations.

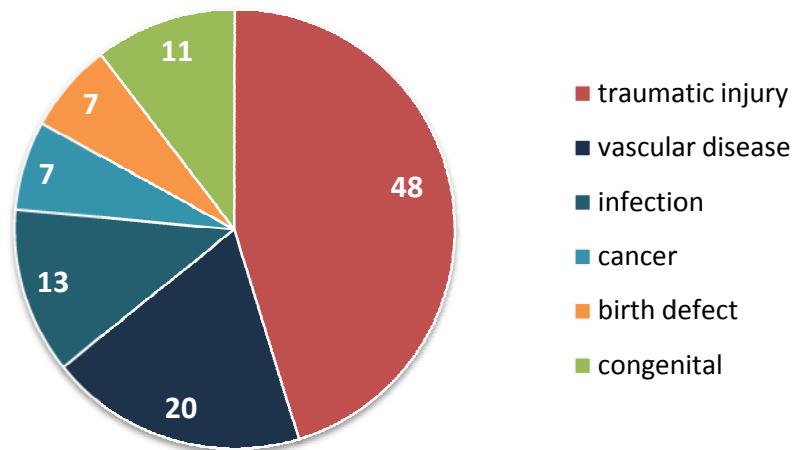


Figure 4: Causes of amputation in sample of 106 questionnaire respondents.

General phantom sensations in people with amputations caused suddenly by traumatic injury (Mdn = 7, IQR = 5-8) were experienced significantly more frequently than by amputees with long-term causes of amputation (Mdn = 5, IQR = 2.5-7; $U = 451.500$, $z = -3.242$, $p = .001$), but there was no difference between the two groups in frequency of phantom limb pain ($U = 568.500$, $z = -.094$, $p = .925$). Although long-term cause amputees experienced significantly more pain prior to amputation ($M = 64.54$, $SD = 36.97$) than sudden cause amputees ($M = 35.40$, $SD = 41.75$; $t_{(85)} = 3.407$, $p = .001$), there was also no significant difference between the two groups in phantom limb pain intensity ($t_{(80)} = -1.255$, $p = .213$).

3. 3. Difference in phantom pain based on non-painful phantom limb phenomena

3. 3. 1. *Mirror-Touch Synaesthesia*: Seeing someone else in pain was reported to cause phantom sensations in 17.65% of cases, and for 32.65% the phantom limb sometimes mimicked the sensations and actions of the intact limb. Synaesthetic mirror-touch sensations – when observing the stimulation or movement of another person induces a similar sensation in the phantom limb – occurred in the phantom limbs of 10.75% of participants when observing another person being touched ($n = 4$), seeing someone execute an action ($n = 2$) or both ($n = 4$). Phantom pain was not experienced more frequently or at a higher intensity by amputees who reported feeling mirrored sensations of touch and movement ($U = 144.000$, $z = -1.664$, $p = .096$, and $t_{(10.14)} = -.326$, $p = .751$, respectively).

3. 3. 2. *Telescoping*: A total of 20.69% of the amputees experienced some form of telescoping. A change in the length of the phantom limb was reported by 19.54% of the

amputees (shorter, $n = 14$; longer, $n = 3$), and change in size was reported by 13.48% (smaller, $n = 10$; bigger, $n = 2$). General phantom limb sensations were experienced more frequently by amputees with telescoped phantom limbs ($Mdn = 7$, $IQR = 7-8$) than those with phantom limbs of normal length and size ($Mdn = 5.50$, $IQR = 2.50-8$; $U = 379.000$, $z = -2.255$, $p = .024$), but telescoping did not affect phantom pain intensity ($t_{(83)} = -1.446$, $p = .152$) or frequency ($U = 335.500$, $z = -1.608$, $p = .108$). Most amputees with telescoped limbs (68.75%) reported that phantom pain was triggered by daily events, whereas significantly fewer amputees with phantom limbs of a normal length (40.68%) reported this association ($\chi^2_{(1)} = 3.985$, $p = .046$).

3. 3. 3. Prosthesis Use: Of the participants surveyed 95.31% of lower-limb amputees and 81.82% of upper-limb amputees reported to currently be using a prosthetic limb, and of these 90.31% and 55.56%, respectively, reported that their phantom limb embodied the prosthesis by occupying the same physical space. There was no difference in phantom pain intensity or phantom pain frequency for lower-limb amputees based on prosthetic limb use ($t_{(75)} = 1.044$, $p = .300$ and $U = 121.000$, $z = -1.249$, $p = .212$, respectively) or embodiment ($t_{(11.60)} = 1.010$, $p = .333$ and $U = 122.500$, $z = -.459$, $p = .212$, respectively); or upper-limb amputees based on prosthetic limb use ($t_{(11)} = .285$, $p = .781$ and $U = 6.500$, $z = -1.50$, $p = .881$, respectively) or embodiment ($t_{(9)} = -1.761$, $p = .112$ and $U = 5.000$, $z = -.764$, $p = .445$, respectively). In lower-limb amputees, but not in upper-limb amputees, phantom sensations started later after amputation in prosthesis users ($Mdn = 2$, $IQR = 1-4$) than in non-users ($Mdn = 1$, $IQR = 1-2$; $U = 169.000$, $z = -2.308$, $p = .021$); whilst in upper-limb amputees, but not in lower-limb amputees, phantom sensations were more frequent in prosthesis users ($Mdn = 8$, $IQR = 7-8$) than in non-users ($Mdn = 6$, $IQR = 1-7$; $U = 3.500$, $z = -2.131$, $p = .033$).

3. 3. 4. Mobility: The ability to move the phantom limb by choice (e.g. wiggle the toes) was reported by 71.43% of the sample, spontaneous phantom limb movement (e.g. to avoid being hurt) was reported by 59.34%, and 47.19% felt as if they could carry out combined movement with the intact and phantom limb together (e.g. gesticulating). Independent samples t-tests found no significant differences in phantom limb pain intensity or frequency based on the ability to move the phantom limb by choice (intensity: $t_{(61.89)} = .769$, $p = .445$; frequency: $U = 479$, $z = -.585$, $p = .559$), instinctively (intensity: $t_{(87)} = 1.10$, $p = .275$; frequency: $U = 580.000$, $z = -.006$, $p = .995$) or in combination with the intact limb (intensity: $t_{(84)} = .143$, $p = .887$; frequency: $U = 489.000$, $z = -1264$, $p = .206$).

4. General Discussion

The present study developed a new questionnaire to examine phantom limb pain and the findings fall in line with many previous investigations into the cognitive and experiential correlates of this phenomenon in amputees. In accordance with previous reports, 94.74% of amputees in our sample experienced phantom limb sensations, and of these 88.89% experienced chronic pain in their phantom limb (Steinbach *et al.*, 1982; Jensen *et al.*, 1983, 1985; Houghton *et al.*, 1994; Wartan *et al.*, 1997; Richardson *et al.*, 2006; Giummarra *et al.*, 2010). The mean intensity of phantom pain (45 millimetres) was slightly lower than some previous ratings of phantom limbs (56 millimetres by Wartan *et al.*, 1997; 55 millimetres by Richardson *et al.*, 2006) and higher than others (16-24 millimetres by Nikolajsen *et al.*, 1997). Frequency patterns were also similar: non-painful sensations were more common than painful ones (Smith *et al.*, 1999), and those with phantom sensations were more likely to experience phantom limb pain (Wartan *et al.*, 1997). The relationship between frequency of phantom sensations, and frequency and intensity of phantom pain and various factors was explored, and the main results are summarised in Table 1.

No relationship was found between pre-operative pain and phantom limb pain, despite the pain persisting for more than six months prior to amputation in most of the amputees, and the similarity in intensity of the pain before and after. This was not the first report of no correlation (Wartan *et al.*, 1997; Davidson *et al.*, 2010), but this brings into question findings that suggested a link between pre-operative and phantom pain. In studies reporting such a link 82-100% of the amputations were of vascular or other long-term origin (Jensen *et al.*, 1983, 1985; Katz and Melzack, 1990; Nikolajsen *et al.*, 1997). Long-term causes of amputation have been found here and in the literature (e.g. Houghton *et al.*, 1994) to be associated with higher levels of pre-operative pain. It is possible that the relationship between pre-operative pain and phantom pain only occurs for populations with extremely high levels of pre-operative pain to begin with.

In line with Houghton *et al.*'s (1994) research, this study also found that despite higher intensities of pre-operative pain in those with long-term causes of amputation, there was no significant difference between the two groups in the frequency or intensity of phantom limb pain. A possible explanation proposed for this is that pre-operative pain may affect the character and distribution of the pain in the phantom, rather than its quantity (Houghton *et al.*, 1994). This could perhaps explain why even though there was no difference in phantom pain between these two groups, there was a difference in the frequency of general phantom

sensations. Those whose amputation was caused suddenly by traumatic injury experienced general phantom sensations more frequently than those who had a long time to prepare for the amputation. This could be because the body schemas of individuals who elected to have an amputation after long-term suffering with a useless and/or painful limb may have already begun to change prior to amputation; whilst for people who experienced their amputation suddenly the missing limb may still form an active part of their body schema after amputation, thus increasing their experience of phantom limb sensations.

Table 1: Summary of relationships and differences in phantom pain intensity, pain frequency and frequency of general phantom sensations with other amputation and phantom attributes.

	Intensity of phantom pain	Frequency of phantom pain	Frequency of general sensations
Tests of Correlation			
Age at amputation		+	+
Time since amputation		+	*
Intensity of pain prior to amputation	+		+
Duration of pain prior to amputation			+
Immediacy of phantom post-amputation			**
Tests of Difference			
Trigger-induced vs. random phantom pain	*		+
Upper- vs. lower-limb amputation			
Above- vs. below-joint amputation	**	+	**
Dominant vs. non-dominant amputation			
Males vs. Females			
Long-term vs. sudden cause of amputation			**
Mirror-touch vs. no synaesthesia		+	
Telescoped vs. normal-sized phantom			*
Prosthesis vs. no prosthesis			
Embodiment vs. no embodiment			
Mobile vs. fixed position			
+ p < .10, * p < .05, ** p < .005			

The matter of what environmental events trigger phantom limb pain hasn't been extensively investigated. Sherman *et al.* (1984) reported that weather change, prosthesis malfunction, mental stress and fatigue were common inducers of phantom pain, and Giummarra, Geogiou-Karitianis, Gibson, Chou and Bradshaw (2006) suggested that the phantom pain was often experienced when the body schema representation was activated or during autonomic arousal. A recent study also showed a link between nocturnal periods of rest with phantom limb pain (Giummarra and Bradshaw, 2010). Giummarra and Bradshaw, (2010) suggested a causal role of dopamine circadian rhythms (Hening *et al.*, 1999) sometimes involved in pain perception (Nestler and Carlezon, 2006) in conditions such as restless leg syndrome. Our results also showed that the most common trigger of phantom limb pain was rest and sleep or bedtime, or during physical or mental stress. The current study is the first to show higher levels of phantom pain intensity in amputees whose episodes of phantom pain are induced by such triggers. These amputees also experienced overall phantom sensations more frequently than those whose phantom pain seemed to occur at random. In contrast to Giummarra and Bradshaw (2010) who found that lower-limb amputees suffer worse night-time pain than upper-limb amputees, the current study revealed that upper-limb amputees were more likely to report an association between phantom pain and specific inducers than lower-limb amputees. Research into triggers of phantom pain is in its infancy. We hope that future research will further address this by investigating the links between pain-inducers, levels of phantom pain and phantom sensations. This could be done by looking into dopamine dysfunction and predisposing factors, such as genetics and structural changes in the cortex of amputees.

The intensity and frequency of phantom limb pain was not found to be affected by most physical/medical amputation factors, such as type of amputation, dominance of amputated limb, prosthesis use or sex of the participant, or non-painful phantom limb phenomena, such as mirror-touch synaesthesia, embodiment or mobility. General phantom sensations were more frequent in individuals with telescoped limbs, but as in Richardson *et al.*'s (2006) results, a link between telescoping and phantom pain was not evident. Phantom pain was more intense and sensations more frequent in amputees where the site of amputation was more proximal to the torso, i.e. above the knee or elbow amputations. Giummarra *et al.* (2010) showed that proximal amputations were associated with higher levels of telescoping, abnormal limb postures and less frequent prosthesis use. These factors may all tie in together as wearing a prosthetic limb has been reported to prevent telescoping (Mayer, Kudar, Bretz and Tihanyi, 2008) and phantom pain (Weiss *et al.*, 1999). As such, the increased

phantom pain in participants with proximal amputations in the current investigation may be because they wear their prosthesis less often than those with distal amputation.

Phantom pain has been previously reported to decrease with time (Jensen *et al.*, 1983, 1985; Houghton *et al.*, 1994), but the current study found no relationship between the amount of time that had elapsed since amputation and the amputees' self-reports of phantom limb pain. However, when scores of phantom pain intensity on one occasion were directly compared to pain scores two years later; a decrease was evident. This emphasises an inevitable weakness of this questionnaire design: the major influence and possible risk of relying on the participants' memories when investigating past experiences. This may also provide an explanation for the lack of correlation between pre-operative pain and phantom limb pain. To take this research a step further the same questionnaire would be distributed after a period of time and questions would ask about current experiences of phantom pain. It would also help to question people prior to amputation to get a more accurate descriptions of pain intensity.

In summary, this study provided insight into phantom limb pain by questioning a large sample of amputees about the intensity and frequency of phantom sensations, and examining other physiological and phantom factors that may be involved. Although there was largely no difference in phantom pain experiences based on type, cause or limb dominance of the amputation, and mirror-touch, embodiment or mobility sensations, light has been shed on the importance of further investigating phantom-pain inducers and individual differences between amputees with trigger-specific pain and those whose phantom pain seems to occur at random. The future sees a large scale exploration of these phenomena both prior to amputation and post-operatively, as well as a behavioural and neuroscientific approach to investigating this.

Paper 2

Mirror-touch synaesthesia in the phantom limbs of amputees

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In mirror-touch synaesthesia merely observing another person being touched causes the observer to experience a touch sensation on their own body. The current study investigates whether this, normally a developmental condition, might be acquired following amputation. Twenty-eight amputees observed 67 videos of touch events and indicated a) whether the video elicited tactile sensations, b) where on the body this was located, c) the intensity of the sensation, and d) whether it was painful. Almost a third of amputees reported a tactile sensation on their amputated phantom limb when watching someone else being touched. In this particular group the sensations tended to be localised on the phantom limb or stump, but were rarely reported elsewhere on the body. This occurred irrespective of the body part seen. The synaesthetic sensations were more intense when real bodies were observed relative to dummies or objects, and when the observed touch was mildly painful relative to non-painful. Although frequency, intensity and cause of phantom limb pain did not appear to determine whether an amputee would report mirror-touch sensations, those who did report it showed greater empathic emotional reactivity. These results suggest that acquired synaesthesia may be linked with sensory loss, arising after amputation, and that highly empathic individuals could be predisposed to strengthening existing pathways between observed touch and felt touch.

1. Introduction

Following amputation, 98% of amputees report a 'phantom' feeling that the missing limb still exists (e.g. Ramachandran and Hirstein, 1998). This is typically explained by assuming that the brain's representation of the body is maintained after amputation (as a sensory-motor 'memory' of the missing limb) and may still be activated from various other inputs that are modified, via plasticity, when the normal somatosensory and proprioceptive inputs from the limb are lost (e.g. Melzack, 1990; Flor *et al.*, 2006). Much of this research has concerned intra-modal plasticity such that adjacent regions of somatosensory cortex may send inputs into the 'silent' region representing the missing limb giving rise to phantom limb pain (Flor *et al.*, 1995) or referred tactile sensations (Halligan *et al.*, 1993). However, there has also been a significant body of research on the role of cross-modal inputs, notably from vision, on phantom limb experiences. For example, if touch is applied to the left hand of a right-arm amputee but such that a mirror reflects the sight of touch into the space of the missing limb, then tactile sensations are reported on the phantom right hand in addition to the intact left hand (Ramachandran and Rogers-Ramachandran, 1996). Phenomena such as this have often been labelled as examples of synaesthesia induced in phantom limbs because a visual input is needed to create the tactile sensation. The present study is also concerned with synaesthesia experienced in phantom limbs, but it differs from the previous example in a number of important respects. It concerns inter-personal sensations induced by watching touch to another human (rather than touch observed within one's own body space) and it is elicited solely from vision without the need for additional touching of the participant's intact limb (Ramachandran and Rogers-Ramachandran, 1996) or stump (Ehrsson *et al.*, 2008).

Mirror systems have been hypothesised to provide a general mechanism for inter-personal sensory and motor correspondences (e.g. Rizzolatti and Craighero, 2004). In the original discovery of mirror neurons, these neurons were found to respond both when a monkey performed an action and when a monkey observed another person performing the same action (Rizzolatti *et al.*, 1996). In humans, evidence for a comparable system has been obtained from increased motor excitability during action observation using transcranial magnetic stimulation (e.g. Fadiga *et al.*, 1995), from functional neuroimaging studies (e.g. Buccino *et al.*, 2001) and from single cell recordings (Mukamel *et al.*, 2010). The studies on action observation have been extended in a number of important ways. It has been argued that comparable mirror systems exist in other domains such as for touch, pain and emotion. Observing others being touched activated, during neuroimaging, somatosensory regions of the

brain (Keysers *et al.*, 2010) and observing others in pain activated the so-called 'pain matrix' including the anterior insulae and anterior cingulate (Singer *et al.*, 2004). The same regions were also active when 'real' touch and pain are experienced. Similarly, perceived threat to a rubber hand was associated with neural activity in the 'pain matrix' but only during conditions of illusory ownership (Ehrsson *et al.*, 2007). Moreover, it has been argued that this inter-personal sharing of feelings may provide a neural basis for certain aspects of empathy (Carr *et al.*, 2003; Leslie *et al.*, 2003). Several lines of evidence support this. In functional neuroimaging studies, self-reported levels of trait empathy may correlate with levels of brain activity when watching others in pain (Singer *et al.*, 2004). Avenanti *et al.* (2009) showed participants images of a body part being injected with a needle and measured cortico-spinal activity. They found a decrease in cortico-spinal activity that was correlated with the pain they believed was being experienced by the person being injected, and was specific to the body part observed. This effect was greater in participants who scored highly on an empathy questionnaire. Similarly, they found in research investigating racial bias that empathically cortico-spinal excitability was reduced when observing pain to a member of the in-group, but not when seeing a member of the out-group in pain (Avenanti *et al.*, 2010).

For most people, observing touch activates the somatosensory system (e.g. Keysers *et al.*, 2004; Ebisch *et al.*, 2008) and may lead to behavioural facilitation/interference of felt touch (e.g. Schaefer *et al.*, 2005; Serino *et al.*, 2008), but this activity is not normally associated with conscious experiences of being touched. However, some people do report tactile experiences on their own body in response to observing touch on others and this has been termed mirror-touch synaesthesia (Banissy and Ward, 2007). Synaesthesia occurs when the stimulation of one sensory modality, such as vision, automatically and immediately induces a conscious sensory experience in another modality, such as touch. The developmental form of synaesthesia, persisting over the lifespan, is thought to have a genetic component (e.g. Asher *et al.*, 2009). Mirror-touch synaesthesia occurs when observing touch to humans but not objects (Blakemore *et al.*, 2005; Banissy and Ward, 2007) and not dummies (Holle *et al.*, 2011). It has been linked, using functional neuroimaging, to hyper-activity in the somatosensory system in response to observing touch (Blakemore *et al.*, 2005). These individuals have heightened tactile acuity (Banissy *et al.*, 2009b) and a higher level of self-reported empathy (Banissy and Ward, 2007). It may have a prevalence of around 1.5% (Banissy *et al.*, 2009a) and is believed to have a developmental rather than acquired origin. However, comparable symptoms may be acquired under certain circumstances. For example, some brain-damaged patients with reduced tactile sensitivity report tactile sensations from observed touch (Halligan

et al., 1996; Halligan *et al.*, 1997). The present study considers whether mirror-touch synaesthesia may be acquired in some people following amputation.

Ramachandran and Brang (2009) empirically investigated mirror-touch synaesthesia in amputees. They reported the cases of four upper-limb amputees who observed an assistant's arm being stroked at 0°, 90° and 180° in front of them. Unlike previous studies (e.g. Ramachandran and Rogers-Ramachandran, 1996; Ehrsson *et al.*, 2008), no actual touch was applied anywhere on their body. They reported that phantom mirror-touch sensations were experienced in 61 of the 64 trials, and that mirror-touch sensations were never experienced in the intact limb. If the observed hand wiggled the sensations were enhanced, and one of their patients experienced cold sensations when observing the assistant's arm being touched by an ice cube. It has been suggested that the mirror system in general may play a role in maintaining a 'normal' representation of the body following amputation (for a review see Giummarra *et al.*, 2007) or in individuals with congenitally missing limbs and phantom sensations who may acquire a 'normal' body representation via inter-personal observation alone (Brugger *et al.*, 2000; Price, 2006).

It is possible that in mirror-touch synaesthesia (e.g. Blakemore *et al.*, 2005) and hyperalgesia (e.g. Bradshaw and Mattingley, 2001) the mirror systems for touch and pain, respectively, exceed the threshold for conscious tactile perception to the extent that individuals report tactile experiences in response to the observation of touch or pain. A review by Fitzgibbon *et al.* (2010b) put forward that the amputees' so called, "synaesthesia for pain" may be the consequence of the removal of the inhibition from a normal pain empathy mirror system caused by a painful or traumatic experience such as an amputation. In a preliminary questionnaire on pain synaesthesia, Fitzgibbon *et al.* (2010a) asked amputees to reflect on past experiences and found that nearly a sixth of amputees surveyed (12/74) recalled experiencing phantom pain when observing or imagining another person in pain. Of these, 91% reported that synaesthesia for pain was not specific to corresponding limb or cause of pain, and 75% claimed that the synaesthetic pain occurred in the phantom regardless of the site of seen or imagined pain.

It is possible that synaesthesia for pain might be relatively common in the general population. Osborn and Derbyshire (2010) presented participants with painful images and movie clips, and found that nearly 30% (31/108) had experienced pain in response to at least one of the images. They classified these participants as 'responders' and compared them in a functional neuroimaging study to 'non-responders' who never reported a sensory feeling in

response to observing the painful stimuli. When observing noxious events as opposed to equivalent neutral events, the responders showed activation in brain regions associated with emotional and sensory pain, whilst the non-responders showed little activation.

In this study, we explore whether amputees report tactile (or painful) sensations in response to observing touch on others. Movie clips showing touch to limbs and faces were recorded and presented on a computer screen. Participants were asked if they felt anything on their own body (or phantom), and were subsequently prompted to report where the sensation was felt, how intense it was, and whether it was painful or not. The visual stimuli were either non-painful or mildly painful (e.g. touch with the tip of a knife) but not strongly painful (as in Osborn and Derbyshire, 2010). This paradigm was adapted from a similar one recently used with normal-bodied mirror-touch synaesthetes (Holle *et al.*, 2011) but the stimuli and questions were adapted to be more appropriate to amputees (e.g. by having more images of limbs and asking participants if the feeling was on the phantom).

2. Methods

2. 1. Participants

Thirty-two individuals with at least one missing limb took part in this study of which three were excluded for not completing the survey and one was excluded because his responses indicated difficulties in understanding the task. The remaining participants (23 male, 5 female) ranged in age from 21 to 71 years (Mean = 54.82 years; SD = 11.86), and consisted of 4 upper-limb amputees and 24 lower-limb amputees. All but three had experienced phantom sensations at some point, and 23 of the amputees still did. The characteristics of these amputees are given in Table 1. Participants were recruited through the Sussex Rehabilitation Centre in Brighton, and had previously completed a questionnaire regarding limb deficiency and phantom limb sensations. Thirty-three control participants took part in a modified version of the experiment (that did not mention phantom limbs) and two were excluded for not understanding the instructions. The control group (15 male, 16 female) ranged in age from 26 to 73 (Mean = 49.42 years; SD = 14.11). The experiment was sponsored by the Life Sciences Ethics Committee at the University of Sussex and approved by the Brighton East Research Ethics Committee of the National Health Service (see Appendix A).

Table 1: Amputation and phantom characteristics of participants.

ID, Sex and Age	Amputation details			Phantom sensations	Mirror-touch sensations	
	Years since	Cause	Side and level		Phantom or stump	Elsewhere
1. M, 45	24	Trauma	Right arm, above elbow	Sometimes	28%*	0
2. M, 64	13	Vascular	Right leg, above knee	Sometimes	28%*	0
3. M, 45	5	Trauma	Both leg, above & below	Sometimes	26%*	0
4. M, 21	3	Trauma	Right leg, below knee	Sometimes	9%*	9%
5. F, 70	3	Trauma	Left arm, above elbow	Permanent	10%*	4%
6. M, 53	17	Trauma	Left leg, below knee	Permanent	6%*	0
7. M, 62	34	Trauma	Right leg, above knee	Sometimes	7%*	0
8. M, 64	2	Vascular	Left leg, above knee	Sometimes	3%*	0
9. M, 63	N/A	Congenital	Left arm, below elbow	None	1%*	1%
10. M, 49	5	Infection	Left leg, below knee	Sometimes	0	13%
11. M, 71	5	Vascular	Left leg, below knee	Sometimes	0	6%
12. M, 49	30	Trauma	Right leg, above knee	Permanent	0	6%
13. F, 38	N/A	Congenital	Left arm, above elbow	None	0	1%
14. M, 70	3	Trauma	Left leg, below knee	Sometimes	0	1%
15. M, 54	5	Infection	Both legs, below knee	Sometimes	0	0
16. M, 66	48	Trauma	Right leg, below knee	Permanent	0	0
17. F, 63	54	Birth defect	Left leg, below knee	Permanent	0	0
18. M, 35	14	Trauma	Right leg, below knee	Permanent	0	0
19. M, 41	23	Trauma	Left leg, below knee	Permanent	0	0
20. M, 53	23	Trauma	Right leg, through knee	Permanent	0	0
21. M, 61	59	Birth defect	Right leg, below knee	None	0	0
22. M, 51	9	Infection	Right leg, below knee	Sometimes	0	0
23. M, 53	10	Trauma	Left leg, above knee	Sometimes	0	0
24. M, 62	6	Infection	Left leg, below knee	Sometimes	0	0
25. M, 50	6	Infection	Left leg, below knee	Sometimes	0	0
26. F, 62	3	Vascular	Left leg, below knee	Sometimes	0	0
27. F, 61	18	Vascular	Right leg, above knee	Sometimes	0	0
28. M, 60	23	Trauma	Left leg, above knee	Permanent	0	0

* These participants were classified as 'responders' as at least one video out of 67 produced a sensation of touch or pain in the phantom (based on classification by Osborn and Derbyshire, 2010).

2. 2. Materials

This study required participants to watch videos which portrayed touch to a real body part, a dummy or an object. In total 34 videos were produced that showed this touch. All (excluding one) of the videos were mirror reversed so that the touch shown in the videos was seen to be applied to both the right and left side. The one stimulus that was not mirror-reversed was a cushion that was touched centrally. Participants therefore viewed 67 videos in total. Of these videos 24 portrayed upper limbs, 20 lower limbs, 10 faces, 10 dummy limbs and 3 objects. All dummy limbs and objects viewed were shown to be poked by a finger. For the other videos the touch seen was made by either another person's finger or an object, namely a knife, feather or flame (that approached close but did not touch). Overall 6 upper-limb videos, 6 lower-limb videos and 6 face videos portrayed touch by an object rather than a finger. In addition to this 4 still images were shown which pictured both a hand and a foot being injected with a needle. These images were the same as those used in the study of Avenanti *et al.*, (2006). Different viewing perspectives were used for videos of limbs. Twenty-four of the videos were shown from an egocentric perspective so that the participant saw the limb as if watching their own limb (or phantom limb) being touched. The remaining 39 of the videos were viewed allocentrically as if watching another individual being touched.

2. 3. Design and Procedure

Participants were told that they would be shown video clips and that they should note if they felt any actual (not imagined) tactile or painful experiences on their body. They were instructed to "Please answer honestly – it doesn't matter if you say 'no' to all of the clips providing this is your honest answer". A repeated measures design was employed so that all participants viewed all of the videos and the videos were randomised across participants so that each participant saw the videos in a different order. Videos were presented one at a time and appeared on the left side of the screen in a box approximately 3.5" x 4" (for a monitor size of 15"). On the right of the screen, Question 1 was displayed asking them if they "Feel anything on your body (or phantom)?" with a binary Yes/No option. All participants were additionally given the option to add any comments that they felt necessary. Each video took approximately 3 seconds to show each touch to the limb/object, and the videos were looped. If they responded 'No' to Question 1 then the intensity was automatically scored as 0 and the next trial started. If they responded 'Yes' to Question 1, participants were then asked three further questions. They were asked about the location where this sensation was felt, choosing

from the following alternatives: 'Phantom Limb', 'Stump', 'Intact Limb', 'Face' or 'Other'. They were asked to rate the intensity of the sensation on a visual analogue scale with integer units from 0 to 10 where 0 was defined as 'No sensation' and 10 as 'Feeling as if you were the person in the video'. Finally, they were asked whether the sensation was painful using a binary (Yes/No) response.

As part of an additional study (conducted in a separate session), amputees completed an empathy questionnaire termed the Empathy Quotient or EQ (Baron-Cohen and Wheelwright, 2004) using the shortened 15-item version of Muncer and Ling (2006). Each item consisted of a statement (e.g. "I really enjoy caring for other people") and responses were given on a 4 point scale ranging from 'strongly agree' to 'strongly disagree'. Two points were given to a strongly empathic response, one point to a moderate empathic response and zero for both moderately non-empathic and strongly non-empathic responses. This version of the questionnaire had three sub-scales termed 'cognitive empathy', 'emotional reactivity' and 'social skills'. The EQ was previously used by Banissy and Ward (2007) to measure empathy in mirror-touch synaesthesia.

The normal-bodied control group was tested after the study with amputees was complete. This required a minor change to the wording of some questions and response options to avoid any reference to 'phantom' or 'stump'. The first question was modified to "Feel anything on your body?", and they were asked to indicate the location for affirmative responses using the categories: right arm, left arm, right leg, left leg, right face, left face and other. (Note: The sidedness could be inferred for most responses given by the amputees since the laterality of the phantom/stump was known).

3. Results

The results are summarised in Figure 1. Some of our control group (Figure 1C) occasionally reported a sensation although it tended to be weak and somatotopic (e.g. leg-to-leg, arm-to-arm). The amputees who reported sensations could be divided into two groups: a group that essentially resembled that found in controls (Figure 1B) and a second, larger, group for whom the sensations gravitated towards the phantom limb and stump (Figure 1A). This group showed a tendency to report sensations more frequently than the other amputee group and controls (see Figure 1a; $t_{(12)} = 1.698$, $p = .115$, and $t_{(15)} = 2.35$, $p = .033$, respectively), and were less likely to have a somatotopic correspondence than the sensations found in the other

amputee group and controls (see Figure 1b; $t_{(12)} = .936$, $p = .368$, and $t_{(15)} = 7.46$, $p < .001$, respectively). The seemingly large difference in somatotopy between the two groups of amputees was due to only one of the five in group B (Participant 11 in Table 1) showing non-somatotopic mapping of the felt sensations. In group A, however, there were 52 trials in which synaesthetic touch was located on the phantom, 29 where they were located on the stump, but only 10 that were reported elsewhere on the body. That is, this group of nine amputees were reporting something that was both qualitatively and quantitatively distinct from other amputees and the normal-bodied sample. As such, further analyses concentrate almost exclusively on this group. We will explore which stimuli tend to evoke these sensations, and we will also consider whether this group differs from other amputees in terms of the characteristics of their amputation history, phantom Limb (e.g. phantom pain), or trait empathy levels.

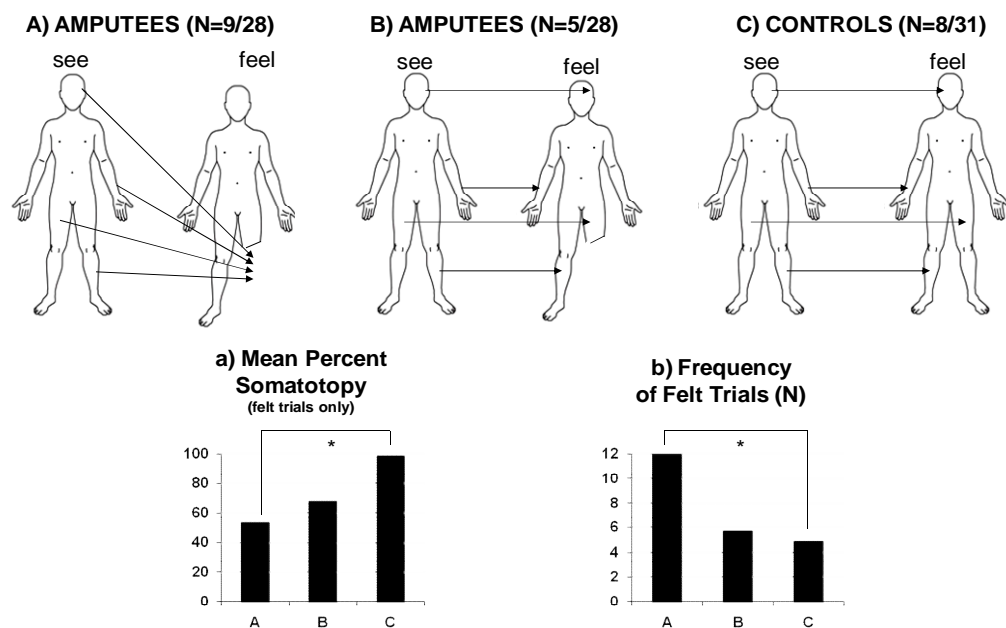


Figure 1: A summary of participants who reported a tactile sensation during the observation of touch; including the average number of trials on which this occurred for these people, and whether the felt touch was reported in the same body part as the observed touch.

3. 1. What Stimuli Trigger Mirror-Touch Sensations in Amputees?

Although the number of trials eliciting sensations was low overall, this may be because only certain types of visual stimuli had a strong propensity for triggering them. For this analysis, the intensity ratings for all stimuli were analysed from the group of nine responders.

A repeated-measures ANOVA indicated a significant difference between real-body, dummy and object target types in elicited sensation intensity ($F_{(2,16)} = 10.017$, $p = .002$). The results are shown in Figure 2. Post-hoc t-tests revealed that real-body targets elicited significantly stronger sensations than dummy targets ($t_{(8)} = 3.540$, $p = .008$) and object targets ($t_{(8)} = 3.353$, $p = .010$). There was no significant difference between dummy targets and object targets ($t_{(8)} = -.510$, $p = .624$). This finding is similar to that reported for normal-bodied mirror-touch synaesthetes who tend to report synaesthetic touch only to observation of touch to a real human body (Holle *et al.*, 2011). Note that the mean intensity values tend to be low due to the inclusion of all trials, including those given an intensity rating of zero.

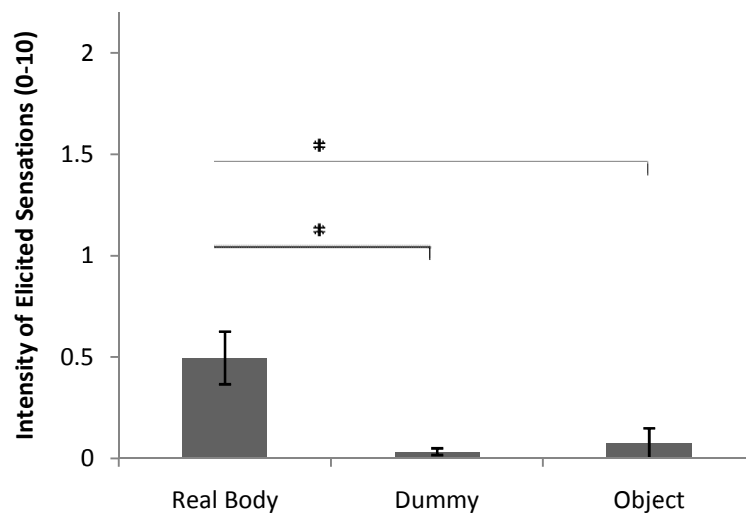


Figure 2: Mean intensity of elicited sensations when observing real body, dummy or objects touched (error bars show ± 1 S.E.M). * $p < .05$

The video stimuli were categorised based on effector type, i.e. the specific object touching the limb in the video. Two stimulus groups were created: one of mildly painful effectors (flame, knife and injection) and another of non-painful effectors (feather and finger). A paired-samples t-test showed that elicited sensations were significantly higher if the effector was mildly painful ($M = 1.22$, $SE = .33$) than if it was not painful ($M = .15$, $SE = .06$; $t_{(8)} = -3.453$, $p = .009$). Analysed as individual effectors, a one-way repeated-measures ANOVA revealed a significant difference between the effector types ($F_{(4, 32)} = 2.711$, $p = .047$). This is shown in Figure 3. Post-hoc pairwise t-tests indicate that the knife elicited stronger responses than the feather and finger ($t_{(8)} = -2.682$, $p = .028$ and $t_{(8)} = -2.709$, $p = .027$, respectively), and the candle

elicited a significantly stronger response than the feather ($t_{(8)} = -2.662, p = .029$). The injection did not yield a significantly different response from any of the other stimuli ($p > .05$), although Figure 2 suggests that these stimuli follow a similar pattern. No other pairwise comparisons were found to be significant ($p > .05$). Although mildly painful stimuli were effective inducers, they did not necessarily induce painful sensations. In addition to being asked about intensity, participants were asked whether the experienced sensations were painful/non-painful (a binary scale). The videos eliciting mirror-touch sensations were also counted with regards to a) whether the video showed mildly painful touch (flame, knife and injection) or non-painful touch (feather and finger), and b) whether the participant reported that the elicited sensations were either painful or non-painful. There were no significant main effects for seeing or experiencing pain ($F_{(1,12)} = 4.133, p = .065$ and $F_{(1,12)} = .146, p = .709$, respectively). There was also no interaction between these ($F_{(1,12)} = 1.83, p = .201$).

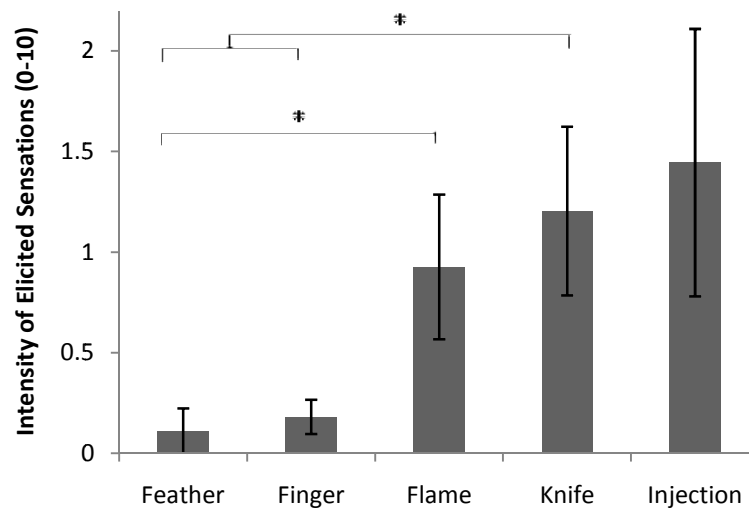


Figure 3: Mean intensity of elicited sensations when observing a feather, finger, candle, knife or injection (error bars show ± 1 S.E.M.). * $p < .05$.

A paired-samples t-test showed no significant difference in intensity depending on whether the perspective of the videos was egocentric ($M = 0.47, SE = 0.11$) or allocentric ($M = 0.33, SE = 0.11; t_{(8)} = 1.453, p = .189$). It is to be noted that there is no difference in intensity between egocentric and allocentric perspectives for normal-bodied mirror-touch synaesthetes, although perspective can modulate the side of the body that it is felt on (Holle *et al.*, 2011).

For this group of amputees, the side of the body that it is felt on is mainly determined by the site of amputation, as previously noted.

A mixed-model ANOVA investigated the between-subjects effect of type of amputation (upper-limb or lower-limb) and the within-subjects effect of body-part touched in video (upper-limb, lower-limb or face). There was no significant main effect of type of amputation ($F_{(1,7)} = .147$, $p = .713$), or of body-part touched in the video ($F_{(2,14)} = 1.149$, $p = .345$). The interaction between these two variables was also not found to be significant ($F_{(2,14)} = .690$, $p = .518$). That is, synaesthetic tactile sensations were just as likely to be reported irrespective of which body part was observed being touched. This result ought to be viewed with caution though as only a small sample of upper-limb amputees was tested.

In summary, synaesthetic tactile sensations in amputees were more intense when real bodies were observed to be touched (relative to dummies and objects) and when the touch was mildly painful (relative to non-painful). It was unaffected by the perspective of the observed body part (allocentric versus egocentric), and it was found for observed touch to different parts of the body. In all these respects it resembled mirror-touch synaesthesia in normal-bodied individuals (Banissy and Ward, 2007; Holle *et al.*, 2011). In one crucial respect it was different: the mapping between observed touch and felt touch was not somatotopic but was, instead, 'captured' by the phantom limb. This suggests that the amputees were not merely saying what they saw (a potential form of confabulation). Similarly, seeing a mildly painful stimulus was just as likely to elicit a non-painful as painful report.

3. 2. What distinguishes amputees reporting 'mirror-touch' from other amputees?

In this section, we examine individual differences between 'responders' reporting mirror-touch sensations on the phantom/stump and 'non-responders'. These analyses are based on the responses given in two questionnaires. Firstly, they had previously filled in a limb deficiency questionnaire. This asked about their amputation and phantom limb experiences. Secondly, a questionnaire asking about trait empathy (the EQ, Empathy Quotient) was given.

Participants were classified into three groups based on the frequency of their phantom limb sensations. Those who in their questionnaire reported never having experienced a phantom were coded as 'None', and those who had a constant feeling of a phantom limb were coded as 'Permanent'. Anyone who had indicated that their phantom sensations came and went at various frequencies was coded as 'Sometimes'. A 3 X 2 Chi-Squared test revealed no

significant difference in the number of responders and non-responders dependent on phantom limb frequency ($\chi^2_{(2)} = 2.22$, $p = .33$).

In the limb deficiency questionnaire, participants had provided a phantom pain score by drawing a line through a 100 millimetres visual analogue scale (VAS) yielding a score out of 100 where 0 represented no pain and 100 represented unbearable pain. An independent-samples t-test showed no significant difference in the mean phantom pain score between responders ($M = 56.11$, $SE = 12.58$) and non-responders ($M = 43.29$, $SE = 9.85$; $t_{(21)} = .807$, $p = .429$). Moreover, a Pearson correlation showed no significant relationship between overall intensity of elicited responses and intensity of phantom limb pain ($r = .430$, $p = .248$, $n = 9$).

Cause of amputation – congenital, trauma, vascular, infection or birth defect – did not lead to a significant difference between responders and non-responders ($\chi^2_{(4)} = 3.69$, $p = .450$). However, there was a significant difference in the responses of upper-limb and lower-limb amputees; whereas all three upper-limb amputees were responders, most of the lower-limb amputees (14 out of 24) were non-responders ($\chi^2_{(1)} = 5.37$, $p = .021$). This finding is interesting but should be treated with caution given the small sample number of upper-limb amputees tested.

Finally, the participants' responses on the empathy quotient questionnaire were analysed in terms of a total EQ score, as well as a score for three empathy subscales: a) cognitive empathy, b) emotional reactivity and c) social skills (Muncer and Ling, 2006). Figure 4 shows that responders scored significantly higher than non-responders on the emotional reactivity empathy subscale ($t_{(18)} = -2.21$, $p = .04$). There was no significant difference between responders and non-responders in total EQ score or on the other empathy subscales ($p > .05$). It is to be noted that this is the same subscale that was previously found to be related to the presence of mirror-touch synaesthesia in the normal-bodied population (Banissy and Ward, 2007).

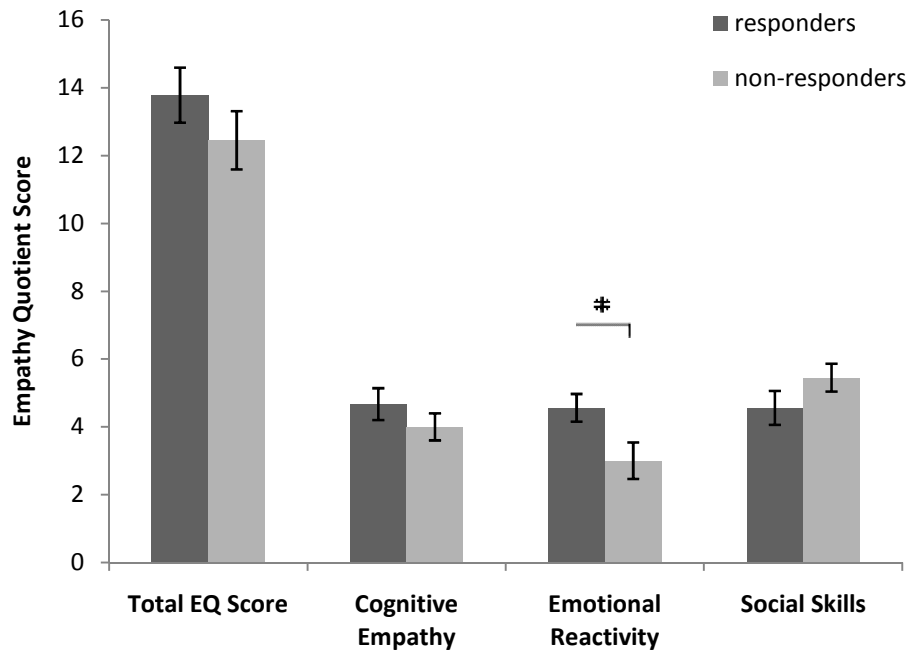


Figure 4: Differences between responders and non-responders on the EQ questionnaire (error bars show ± 1 S.E.M.). * $p < .05$.

4. General Discussion

This study was motivated by anecdotal reports of phantom limb sensations triggered by inter-personal observation. For example, some of the amputees in our sample had previously noted that "seeing someone get hurt causes pains in my stump" and "sometimes seeing someone else move their arms causes my phantom to imitate theirs". It was also motivated by recent studies (e.g. Ramachandran and Brang, 2009; Fitzgibbon *et al.*, 2010a) and reviews (e.g. Fitzgibbon *et al.*, 2010b) concerning synaesthesia for pain and synaesthesia for touch in amputees. We showed our sample of amputees movies of people, dummies and objects being touched and asked them to report any experiences of touch (or pain) that they felt. We identified a group of 9 'responders' who tended to report sensations on the phantom or stump but rarely anywhere else. The synaesthetic sensations tended to be elicited by touch to humans (but not dummies or objects) and for mildly painful stimuli relative to non-painful stimuli. In this respect, they were similar to normal-bodied mirror-touch synaesthetes (Holle *et al.*, 2011) although they were not necessarily quantitatively similar. That is, the normal-bodied mirror-touch synaesthetes tended to report tactile sensations on a higher proportion of trials than the amputees did. However, there is one crucial difference between these groups. Normal-bodied mirror-touch synaesthetes reported touch on the face when observing

touch to a face, and touch to the arm when observing touch to the arm, etc. That is, somatotopy was preserved between observed touch and synaesthetic touch. This was not the case in amputees for whom the synaesthetic touch was almost always felt in the phantom/stump irrespective of the body part observed.

Although the findings were largely based on self-report data, we believe that the data cannot be explained as the amputees saying what they saw (rather than what they felt), or saying what they thought we wanted to hear (a compliance effect). Their reports often deviated from what they saw (e.g. seeing touch to an arm being reported as a sensation on the phantom leg). There was also high agreement within the group of responders suggesting that the pattern was robust. Another possible counter-argument is that the sensations were real but they were not induced; for instance, they could reflect spontaneous changes in phantom limb sensations over time (of fluctuations in attention directed at the phantom). However, we consider this unlikely because some stimuli were more prone to elicit responses than others. We would expect the pattern to be more random if they were a result of spontaneous fluctuations. Moreover, neither the frequency nor intensity of phantom limb sensations discriminated responders from non-responders.

What caused synaesthetic sensations in the amputees to gravitate towards the affected limb? There are several possibilities. One is the presence of pain in that region. Another is the loss of (veridical) sensation in that region. We could find no evidence that the intensity or frequency of phantom limb pain was related to the presence of synaesthetic experiences. However, it would be interesting to repeat the study using visual stimuli associated with higher levels of pain. For instance, Osborn and Derbyshire (2010) used images of broken limbs. Although we cannot discount the role of pain, other types of acquired synaesthesia are almost always linked to sensory loss. For example, synaesthetically induced phosphenes from sound (e.g. *Afra et al.*, 2009) and touch (Armel and Ramachandran, 1999) have been reported in acquired blindness of peripheral origin. In patients with visual field defects, synaesthetically induced phosphenes may be localised entirely within the blind region (*Jacobs et al.*, 1981). A recent neurological case reported synaesthetic touch in response to sounds following a thalamic lesion (*Ro et al.*, 2007). The patient had reduced tactile sensitivity down one side of the body and the synaesthetic tactile experiences tended to be localised on this affected side. As such there is a general tendency for acquired synaesthesia to be linked to sensory loss (including localised sensory loss) and amputation may be just one example of this. One prediction is that we should find similar cases of acquired mirror-touch synaesthesia in normal-bodied people with reduced limb sensation (e.g. brachial plexus injury) but not

necessarily in normal-bodied people with significant limb pain but normal sensation (e.g. extreme cases of deep vein thrombosis). It is interesting to note that the phenomenon of 'mitempfindung', the simultaneous sensation of touch at two different locations of the body that sometimes occurs after sensory loss (Schott, 1988), is not somatotopically consistent (Evans, 1976), and may be more common amongst synaesthetes (Burrack *et al.*, 2006).

The mechanism that could support the emergence of acquired mirror-touch synaesthesia is cross-modal plasticity between visual (or visuo-tactile) regions and somatosensory regions. This kind of plasticity is assumed to occur in two phases: an initial unmasking (or disinhibition) of existing multi-sensory pathways followed by longer-term formation of new synaptic connections (e.g. Pascual-Leone *et al.*, 2005). Acquired synaesthesia following sudden blindness can emerge in as few as 1-3 days (e.g. Afra *et al.*, 2009) which is consistent with this fast acting mechanism, and it would be interesting to know when mirror-touch synaesthesia emerges following amputation.

Although the presence of mirror-touch synaesthesia in amputees was not predicted by characteristics of their phantom limb, it was predicted by one measure of empathy, namely 'emotional reactivity'. This sub-scale measures automatic emotional reactions directed towards other people (e.g. sharing their sadness) rather than the more cognitive aspects of empathy (e.g. thinking about feelings), and it was also found to be higher in normal-bodied mirror-touch synaesthetes relative to controls (e.g. Banissy and Ward, 2007). In a study that compared patients with lesions to the ventromedial prefrontal cortex, associated with cognitive perspective-taking, to patients with inferior frontal gyrus lesions, associated with emotional contagion, Shamay-Tsoori *et al.* (2009) found evidence to suggest that there are two dissociate pathways for these types of empathy. Differences in empathy revealed themselves in the extent to which individuals responded, physiologically, to seeing others in pain (Singer *et al.*, 2004; Avenanti *et al.*, 2009; Singer, 2009; Avenanti *et al.*, 2010). Our claim is not that high empathy is a necessary condition for mirror-touch synaesthesia to occur following an amputation, but rather that these individuals have a head-start when it comes to modifying existing pathways linking observed touch to felt touch.

To conclude, we propose that as in mirror-touch synaesthesia, the somatosensory system of nearly a third of amputees reaches supra-threshold levels so that observed touch manifests as felt touch. Unlike normal-bodied mirror-touch synaesthetes the sensations are not somatotopically mapped, but usually occur in the phantom limb or stump. Such acquired synaesthesia may be the consequence of an unmasking of usually inhibitory pathways and the

formation of new synaptic connections caused by the sensory loss associated with amputation. By exploring the situations leading to sensations and the characteristics of the experienced touch, the current study has enhanced our understanding of visuo-tactile interaction in amputees with phantom limbs.

Paper 3

Does amputation alter body schema? Perception of apparent biological motion in amputees with phantom sensations

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The current set of experiments aimed to investigate if the ability to perceive action by those with acquired amputation is determined merely by the presence of phantom sensations (Funk *et al.*, 2005), or by specific qualities of the phantom that would be indicative of a normal body schema, such as mobility and solidity. In apparent biological motion one normally perceives rate-dependent paths of motion. With a short interval between two rapidly-alternating body images, perception is of the limbs taking the most direct path regardless of whether it is physically possible; at longer intervals the limbs follow a biomechanically possible trajectory. Using leg stimuli, Experiment 1 successfully replicated previous findings in a normal-bodied sample (Shiffrar and Freyd, 1990), but no differences were found between 'Front', 'Side', 'Self' and 'Partial' perspectives. For the 'Self' and 'Other' perspectives in Experiment 2 all the participants perceived the biologically possible trajectory more frequently as the inter-stimulus interval was increased, but this effect was significantly weaker in the amputees than in the controls. Moreover, when the 'Partial' view of the legs was presented before the others, neither group showed a preference for perceiving the possible or impossible. This indifference was also observed for the 'Object' perspective in Experiment 3, where again amputees showed a dampened rate-dependent effect relative to controls for the 'Self' and 'Other' perspectives. However, this difference between the groups did not reach statistical significance. A similar pattern was found when the participants viewed 'Arms' stimuli, suggesting that body schema remains globally intact after amputation. Furthermore, no differences in perceived motion were found based on the mobility or solidity of the phantom limb. Thus, we conclude that either change to body schema does not impact on biological motion perception, or that particular qualities of the phantom do not indicate abnormal body schema.

1. Introduction

The ability to interpret the actions of other people is believed to be highly dependent on the mental representation we possess of our own bodies. Evidence from normal-bodied participants indicates a clear link between action perception and action execution (see Grezes and Decety, 2001, for a meta-analysis; for a review see de Vignemont and Haggard, 2008). People are better at recognising their own movements (Beardsworth and Buckner, 1981; Loula, Prasad, Harber and Shiffrar, 2005) and the output of these (Knoblich and Flach, 2001; Knoblich and Prinz, 2001) than those of others. Similarly, the action one is carrying out when watching the body of another may influence one's perception of the observed action (Reed and Farah, 1995; Hamilton, Wolpert and Frith, 2004; Jacobs and Shiffrar, 2005). Clinical populations provide insight into the notion of a unified representation of perception and execution by allowing for the investigation of the consequence to one when the other is impaired. In hemiplegia, for example, paralysis or paresis is experienced on one side of the body as a consequence of a lesion in the contralateral brain hemisphere. Serino *et al.* (2010) compared stroke patients with hemiplegia to stroke patients without it on point light animation tasks. They found poorer performance in the hemiplegics for action recognition when watching actions produced by the arm equivalent to the paretic arm when compared to observing actions produced by the non-paretic arm. Non-hemiplegic stroke patients did not show this difference in impaired performance. Thus, it seems that action perception suffers when action execution is compromised (Serino *et al.*, 2010), and the ability to interpret biological motion is dependent on the ability to execute such motion.

In hemiplegia it is *brain* abnormalities that cause perceptual differences in the mental representation of a body schema. Would damage to the *body* affect body schema integration in a similar way as damage to the brain? The body schema, a term coined by Head and Holmes (1911-12), is a multi-modal representation of the body based on proprioceptive, vestibular and visual input. To explain how these various inputs become a unified representation of the body in the brain, and to elucidate the role of the body schema in phantom limb sensations, Melzack (1990, 1992) introduced the concept of a neuromatrix. The thalamocortical and limbic loops involved here produce a specific cyclical pattern of neural pathways which are genetically innate in origin, but are eventually altered by the sensory experience of our environment. It is the neuromatrix that provides us with a unitary integrated sense of self. Even after limb amputation, the neuromatrix underlying the body schema remains intact, thus producing the sensation of a phantom limb (Melzack, 1990, 1992).

Of amputees, 95-100% experience a phantom sensation that the missing limb is still present (Simmel, 1956), and 80% of amputees describe pain in their phantom limb (Sherman, 1994). Immediately following amputation the brain continues to send output to the missing limb which results in automatic phantom limb sensations in at least 75% of cases (Moser, 1948; as cited by Ramachandran and Hirstein, 1998). Melzack's (1990) theory of body schema suggested that the phantom is merely a neural memory of the absent limb, and it is possible that phantom pain may reflect the pain experienced in the event that caused the amputation to occur (Simmel, 1962; Katz and Melzack, 1990). More recently an alternative, although not incompatible, view proposed that phantom sensations arise as a consequence of changes that may occur in the brain following amputation (Ramachandran, Stewart and Rogers-Ramachandran, 1992; Halligan, Marshall, Wade, Davey and Morrison, 1993). The suggestion was that when a limb is lost the cortical region in which it is represented is "taken over" by the neighbouring cortical areas by "unmasking" of previously inhibitory synaptic pathways (Wall, 1977). For example, in the case of an arm amputation, connections in the primary somatosensory cortex between the hand region and the face and stump regions would become unveiled so that touch to the face or stump would activate the representation of the arm (Ramachandran *et al.*, 1992; Halligan *et al.*, 1993). According to Ramachandran and Hirstein (1998) it is the proprioceptive and tactile inputs to these neighbouring regions that reawaken the missing limb's representation which survives in the form of a phantom limb. Associations have also been found between the extent of cortical reorganisation and the quantity of phantom pain (Flor *et al.*, 1995; Lotze, Flor, Grodd, Larbig and Birbaumer, 2001; Flor, Nikolajsen and Jensen, 2006).

However, neither possessing a neural memory nor undergoing cortical reorganisation can fully explain all phantom limb phenomena. Up to 20% of individuals with congenitally missing limbs experience phantom sensations (Melzack, Israel, Lacroix and Schultz, 1997) despite never having possessed the limb or therefore undergone cortical reorganisation. Some people with phantoms feel they have the ability to move and use these limbs, for example, to gesticulate whilst talking (e.g. Ramachandran, 1993; Brugger *et al.*, 2000). Moreover, observing other people's actions can trigger involuntary phantom sensations both in amputees (Henderson and Smyth, 1948; Ramachandran and Brang, 2009) and individuals born with missing limbs (Melzack *et al.*, 1997). In extreme cases some amputees describe experiencing phantom pain whilst observing painful stimuli (Fitzgibbon *et al.*, 2010a; Fitzgibbon, Giummarra, Georgiou-Karistianis, Enticott and Bradshaw, 2010b). Similarly, in using a mirror box, a common therapy by which patients observe the reflection of their intact limb in place of the

missing one, the phantom mimics the movement of and the sensations to the intact arm as the two arms remain spatially coupled (Ramachandran and Rogers-Ramachandran, 1996). For these amputees the phantom often feels as though it is stuck in a certain position, which cannot be explained by a remembered neurosignature, as the limb they used to possess had the ability to move volitionally and reflexively.

The mirror system may offer an alternative, or perhaps complementary (see Price, 2006), explanation for some of these issues. Rizzolatti, Fadiga, Fogassi and Gallese (1996) discovered neurons in the monkey's brain that fired in response to both executing and observing goal-oriented actions, and it has been postulated that a similar network of neurons, termed the mirror system, exists in humans (Gallese, 2001; Rizzolatti and Craighero, 2004). A review on the topic by Giummarra, Gibson, Georgiou-Karistianis and Bradshaw (2007) proposed that there must be something external, and perhaps visual, influencing phantom sensations that goes beyond the internal changes that take place in the cortex. It is possible that a human mirror system, equivalent to the mirror neurons reported in monkeys (Rizzolatti *et al.*, 1996; Umiltà *et al.*, 2001), reinforces the representation of the body in the brain and may continue to do so even if a limb has been amputated. Congenital phantom sensations could have evolved by the observation of other people's limbs and thus maintained by embodying these empathically perceived experiences into their own body schema (Giummarra *et al.*, 2007). The mirrored sensation from the intact limb to the phantom when using a mirror box could be explained as the visual system reinforcing pre-existing connections across the corpus callosum via supra-threshold mirror system activity (Calford, 1991). Similarly, for amputees who experience their phantom as stuck in a certain position, this may reflect the last position they saw their limb in prior to amputation (Katz and Melzack, 1990).

To indirectly test whether phantom sensations rely on a mirror system, and to see if an integrated representation for perception and action is dependent on an intact unified body schema, Funk, Shiffrar and Brugger (2005) compared two people born with no arms on their perception of apparent biological motion. Original studies of apparent motion (e.g. Burt and Sperling, 1981) demonstrated that when an image of a single item, such as a dot on an otherwise blank screen, rapidly alternated with an image of the same item in another location on the screen, the perceived experience is of the item moving via the shortest possible route from the first location to the second. Shiffrar and Freyd (1990), however, showed that this is not always the case; when the apparent motion was produced by alternating images implying biological motion, the path of perceived motion was dependent on anatomical and physical joint and solidity constraints. When the interval between the two stimulus presentations was

brief (e.g. 150-350 milliseconds), observers tended to see the moving limb as taking the most direct route from one position to the other, like the dot moving in the simpler versions of apparent motion experiments (e.g. Burt and Sperling, 1981), regardless of whether this defied the biomechanical capabilities of the human body. But at greater inter-stimulus intervals (ISIs; e.g. 550-750 milliseconds) the apparent movement would only follow the shortest path of motion if it was consistent with the anatomical and physical constraints of the human body. This is because the stored kinaesthetic knowledge of biomechanical movement constraints requires enough processing time for a cross-sensory visuomotor interaction. This notion is supported by a positron emission tomography study that showed increased premotor and inferior parietal cortex activity when the biologically possible route was perceived, but not when the observer perceived the shortest route of motion (Stevens, Fonlupt, Shiffrar and Decety, 2000). These cortical regions are often associated with the perception of biological movement (e.g. Farivar, 2009) and mirror-system activity specifically (Buccino *et al.*, 2001; Rizzolatti and Craighero, 2004; Calvo-Merino, Glaser, Grazes, Passingham and Haggard, 2005). Shiffrar and Freyd (1993) explained that it is evolutionarily adaptive to have the ability to predict the actions of others, and thus incorporating biomechanical constraints into our body schema enables us to anticipate the immediate future.

How would individuals with missing limbs perform on a task involving apparent biological motion? Is the ability to interpret the actions of others dependent on having an intact body, or perhaps an intact body schema? Funk *et al.* (2005) compared two individuals born without arms by employing the apparent biological motion paradigm (Shiffrar and Freyd, 1990, 1993) to investigate how having phantom limb sensations might affect the interpretation of observed limb movement. The key difference between the two participants was that despite the congenital cause of the limb disfigurements, one experienced vivid phantom sensations of possessing the missing arms, whereas the other experienced no such sensations. The authors found that the participant who could sense her missing arms showed a similar pattern of results to control participants, in that as the ISI increased so did the percentage of trials in which the anatomically plausible motion path was perceived. Conversely, the individual without phantom arms did not show a difference in perception across the various ISIs, and moreover he consistently reported perceiving the short and biomechanically impossible route of motion. These findings suggest that normal perception of action is dependent on having a normal body schema, as exhibited by the possession of phantom sensations. Perhaps the origin of this body schema arises from the activation of a

mirror-like system that matches observation and execution of actions (Grezes and Decety, 2001; Rizzolatti, Fogassi and Gallese, 2001; de Vignemont and Haggard, 2008).

Thus it seems that having a complete body schema may determine changes to the visual perception of human bodies in people with a missing limb; however, this altered perception still does not explain why some congenital cases of limb malformation experience phantom limbs, and hence an intact body schema, whilst others do not. The current research looks at the perception of apparent biological motion in a group of amputees, all of whom experience phantom limb sensations. In accordance with Melzack's (1990) theory of the neuromatrix and Giummarra *et al.*'s (2007) mirror system hypothesis, the experience of phantom limbs by the amputees would be indicative of a preserved neuromatrix and/or mirror system. Ergo, their perception of apparent biological motion ought to be similar to that of the normal-bodied population.

A further aim here is to determine whether certain *qualities* of the phantom limb, such as mobility and solidity, lead amputees to show a different pattern of results in the perception of apparent biological motion. As a normal body schema would presumably consist of a solid limb which could be moved both volitionally and reflexively, it would be of particular interest to discover if those with more 'ghostly' phantoms or those whose phantoms were stuck in a fixed position would show a different pattern of results to the rest of the amputees. A large body of research has pointed to individual differences in phantom limb sensations (Melzack, 1990; Ramachandran and Hirstein, 1998; Giummarra *et al.*, 2007), and Funk *et al.* (2005) specifically note "the importance of each individual's history of phantom sensations" (p. 345), but further investigation of these experiences is often neglected.

Moreover, this study will also be the first to investigate, in amputees and control participants, the perception of apparent motion when viewed from the 'Self' versus 'Other' perspective. Even if they show a similar pattern to controls when observing other people's bodies, amputees might see the limbs as taking the shortest path through each other when presented with images which suggest they are looking down upon their own limbs, as they have the knowledge that their phantom limbs are capable of moving through their intact limbs. We seek to deepen the understanding of body schema and action perception by examining specific qualities of phantom limb sensations, and determining whether viewpoint affects the way in which action is perceived.

2. Experiment 1

In order to replicate previous findings and establish baseline results for our stimuli and ISIs, the first experiment preliminarily examined apparent biological motion in normal-bodied individuals. Whilst Funk *et al.* (2005) used two individuals born with no upper-limbs, the current study aimed to increase the sample size and thus targeted lower-limb amputees as this form of amputation is generally more common. In creating the stimuli of lower-limb apparent motion, however, it became evident that creating a variety of stimuli with two alternative trajectories of apparent motion based on joint constraints was not possible. As such we produced stimuli where the long path of apparent motion between one of the pair to the other had to overcome a solidity constraint (the alternative suggested by Shiffrar and Freyd, 1990). In every pair of stimuli the shortest trajectory of movement involved one leg passing through the other one, whilst in the long trajectory the moving leg had to move around the stationary one.

The experiment replicated two conditions utilised in previous studies ('Front' and 'Partial') and introduced two new conditions ('Side' and 'Self'), yielding four conditions in total. The first condition, 'Front', presented stimuli similar to those used by Shiffrar and Freyd (1990); legs appeared from a straight-on view and produced the percept of one leg moving either around the other due to solidity constraints or chopping through it. In line with preceding research it was hypothesised that perceiving the 'around' path of movement would increase as the inter-stimulus interval increased.

As pilot stimuli revealed that the 'through' motion path was nearly always perceived for 'Front' stimuli, a new condition was introduced in which the path of motion that the moving leg must follow was never occluded by the stationary leg. This condition was termed 'Side' as all stimuli involved viewing the model's legs in profile. It was hypothesised that as the trajectory that the legs must follow could be observed at all times, the 'through' path would less likely be the default in this condition as it was for the pilot 'Front' stimuli.

The third condition, 'Self', introduced the difference between mirroring another's actions and perceiving them as one's own. The aim was to investigate whether the 'around' path would be perceived more frequently than in the 'Front' condition, in normal-bodied controls, because the actions did not need to be mirrored.

A final condition, 'Partial', was added at a later date during a separate testing session to act as a control condition. This condition involved a cropped close-up of the stimuli

presented in the 'Front' condition and has been shown, like non-biological stimuli, not to be effected by biological constraints in previous experiments (e.g. Chatterjee, Freyd and Shiffrar, 1996). It was therefore predicted that perceiving the 'around' path would not increase as the inter-stimulus interval increased and the 'through' path would normally be observed because like objects these images have no joints or biological constraints. This condition was added post-hoc as all other conditions yielded an increase in percentage perceived around with increase of inter-stimulus interval, and this condition was proposed to act as a control. As such an ISI x view interaction was expected such that the 'Partial' view would not vary with inter-stimulus interval while the other three views did.

2. 1. Method

2. 1. 1. *Participants:* Seven postgraduate students at the University of Sussex volunteered for this preliminary study. The participants (4 male, 3 female) ranged in age from 21 to 29 years (Mean = 24.7 years; SD = 2.6). The experiment was approved by the Life Sciences Ethics Committee at the University of Sussex.

2. 1. 2. *Materials:* The set of stimuli consisted of pairs of colour photographs of legs in various positions. One leg was wearing blue tights and the other pink tights in order to increase the contrast between the two legs. The pairs represented the start and finish points of lower-limb movements, such as legs crossing and uncrossing, which could be interpreted in two ways, i.e. as one leg moving around the other or moving through it. Four types of images were used depicting the legs from four various points of view: 'Front', 'Side', 'Self' and 'Partial' (for examples of each see Figure 1). The stimuli were presented in E-Prime 2.0 Professional, and the photographs were edited in Adobe Photoshop CS2. The experiment was displayed in a dark cubicle on a 15" centimetre monitor at a distance of approximately 60 centimetre from the participant.



Figure 1: Example stimuli from 'Front', 'Side', 'Self' and 'Partial' perspectives.

2. 1. 3. Design and Procedure: The four views were presented in separate blocks and each block contained four different stimulus pairs. The same four position pairs were photographed for the four different views, e.g. Figure 1 shows one foot crossing through the other ankle in the four various conditions. Pilot data revealed no significant difference between the four pairs of stimuli in each condition ($p > .05$). Within each trial the photograph pairs were presented in cycles of 10 alterations where each image was displayed for 100 ms and separated by one of four ISIs: 50, 250, 450 and 650 milliseconds. These ISIs were chosen because they were found to produce apparent motion perceptions in pilot data. In every block each of the four stimulus pairs was presented twice at every ISI yielding 32 trials per block. Trials were randomised by stimulus and ISI in all blocks. At the end of every trial participants were instructed to make a forced choice as to whether they perceived the legs moving 'around' or 'through' each other, and told to indicate this by button press of either 'A' or 'T', respectively. The blocks were presented twice in the following order: 'Front', 'Side' and then 'Self'. The 'Partial' condition was also presented twice, but independently at a later date.

2. 2. Results and Discussion

For each of the conditions the number of times the 'around' path of apparent motion was chosen at each ISI was calculated for every participant. In Figure 2 these data are plotted as the mean percentage of occasions where the participants reported observing the 'around' path at each ISI for all four conditions. A repeated-measures 4 (views) x 4 (ISIs) ANOVA revealed a significant main effect of ISI ($F_{(3,18)} = 34.57, p < .001$), indicating that as the delay between stimulus presentation increased so did the perception of biologically possible limb

movements. However, only a trend was found for the view variable ($F_{(3,18)} = 2.89$, $p = .064$) and no interaction ($F_{(3,54)} = .470$, $p = .888$) was revealed.

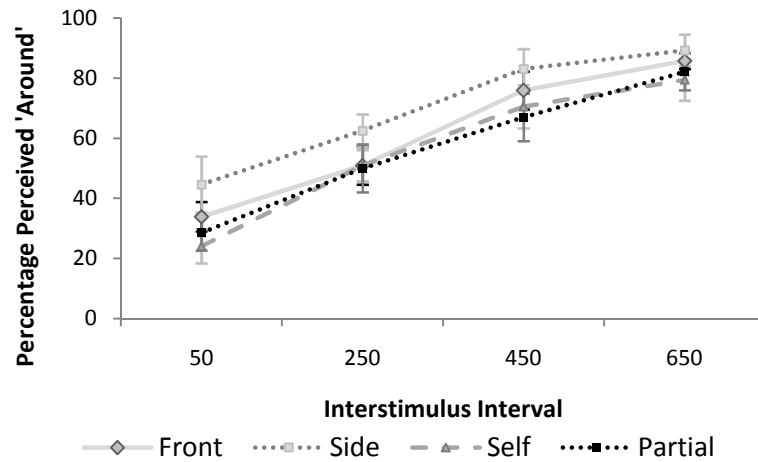


Figure 2: Mean percentage of 'around' path perceptions of apparent motion for various view conditions at increasing levels of ISIs for normal-bodied participants.

The findings for the 'Front', 'Side' and 'Self' conditions followed general predictions and successfully replicated previous research (e.g. Shiffrar and Freyd, 1990) by reinforcing the notion that given enough processing time stored kinaesthetic knowledge may be employed for interpretation of the movement in the biologically possible trajectory (Shiffrar and Freyd, 1993). The 'Side' condition, although not significantly different from the others, did appear to gravitate towards being perceived more often than the other conditions in the anatomically possible way. This may be because the trajectory which the limb would take for the short path, as well as the long path, was visible to the participants at all times. However, the results of the 'Partial' condition did not fall in line with predictions. It was expected that because observers were not able to see the legs as a whole they would perceive the 'Partial' condition in a similar fashion to objects (as in Chatterjee *et al.*, 1996), and thus not show an increase in perceiving the 'around' path with increasing ISIs. It is possible, though, that this is because the 'Partial' condition was only tested after the other conditions; the pre-exposure of the observers to the other conditions in which they could see the whole legs may have caused the inference of the legs' body schema onto the stimuli in the 'Partial' condition.

In all four conditions perception of apparent biological motion was modulated by the temporal interval between stimulus presentations. In a similar vein to original findings by Shiffrar and Freyd (1990, 1993), we found that large intervals permitted access to kinaesthetic

knowledge of the body's biomechanical constraints, whereas rapidly alternating stimuli caused participants to perceive the shortest trajectory of motion (Shiffrar and Freyd, 1993).

Experiment 1 produced reliable results for our stimuli in normal-bodied participants, and showed no difference dependent on the view from which the limbs were observed, i.e. there was no difference between the trend produced by the self and other perspectives. This suggests that processing the view of other people's legs in action takes place in a similar fashion, and perhaps uses the same system, to the way we process movement in our own legs (Grezes and Decety, 2001).

3. Experiment 2

Experiment 1 showed a significant increase in the percentage of times that normal-bodied participants perceived the legs as moving around each other as the ISI was increased; Experiment 2 aims to investigate whether this was also the case in amputees, or if having undergone a physical change to the body also affects the perceptual processing of other people's bodies. It is possible that despite having not found a significant difference between the different viewpoints in the general population, amputees would show a difference here. Namely, amputees may see the legs going through each other more often in the 'Self' condition as their phantom limbs are physically capable of cutting through their intact limbs and occupying the same physical space. In order to prevent a pre-exposure bias for the 'Partial' condition, Experiment 2 set out to repeat the last experiment but with the 'Partial' condition presented before 'Front', 'Side' and 'Self'. The remaining conditions were fully counterbalanced between participants to prevent any other possible order effects. The 'Partial' condition was not integrated into the counterbalancing so that the body schema of "legs" could not be mapped onto the obscure stimuli, thus maintaining their object-like qualities.

3. 1. Method

3. 1. 1. *Participants:* Thirteen individuals with at least one lower-limb amputation took part in this study (three participants had undergone bilateral amputation). The participants (5 male, 8 female) ranged in age from 34 to 85 years (Mean = 62.15 years; SD = 15.86). All participants had experienced phantom sensations at some point, and further

characteristics of these amputees and their phantom sensations are given in Table 1. Participants were recruited through the Sussex Rehabilitation Centre in Brighton, and had previously completed a questionnaire regarding limb deficiency and phantom limb sensations. Eighteen normal-bodied control participants who had not taken part in Experiment 1 underwent this study. The control group (7 Male, 11 Female) ranged in age from 20 to 82 (Mean = 55.55 years; SD = 18.44). Four of the controls were undergraduate Psychology students at the University of Sussex and were reimbursed with course credits for their time. The experiment was sponsored by the Life Sciences Ethics Committee at the University of Sussex and approved by the Brighton East Research Ethics Committee of the National Health Service (see Appendix A).

Table 1: Amputation and phantom characteristics of participants.

ID, Sex and Age	Amputation details			Phantom sensations
	Years since	Cause	Side and level	
1. F, 34	22	Cancer	Right, above knee	Permanent
2. M, 42	20	Trauma	Right, below knee	Permanent
3. M, 43	4	Trauma	Both, above & below	Sometimes
4. F, 62	47	Cancer	Right, above knee	Sometimes
5. F, 67	16	Trauma	Left, below knee	Sometimes
6. F, 73	8	Trauma	Right, above knee	Sometimes
7. M, 53	1	Vascular	Right, below knee	Sometimes
8. F, 73	2	Vascular	Right, below knee	Sometimes
9. F, 85	1	Infection	Both, above knee	Sometimes
10. M, 68	2	Trauma	Left, below knee	Sometimes
11. M, 53	4	Infection	Both, below knee	Sometimes
12. F, 77	5	Vascular	Left, below knee	Sometimes
13. F, 78	15	Cancer	Right, below knee	Sometimes

3. 1. 2. *Materials:* All materials used were identical to those in Experiment 1.

3. 1. 3. *Design and Procedure*: These were identical to those of Experiment 1 with the exception that the 'Partial' condition was presented immediately *prior* to the 'Front', 'Side' and 'Self' conditions, and these conditions were fully counterbalanced between participants, yielding six possible orders of presentation. Testing of each participant took place in one sitting and lasted approximately half an hour.

3. 2. Results and Discussion

The data were treated similarly to Experiment 1 and can be found plotted for amputees and controls as a percentage perceived 'around' path for each view in Figure 3. There was no significant difference between the 'Front' and 'Side' perspectives at the different ISIs when averaged across the two groups ($F_{(3,87)} = 1.983$, $p = .122$), so these were collapsed into a single 'Other' condition by averaging across the 'Front' and 'Side' raw data. A mixed-model 2 (groups) x 3 (views) x 4 (ISIs) ANOVA revealed a significant main effect of ISI ($F_{(3,87)} = 15.088$, $p < .001$) indicating the increase in all participants' perception of the anatomically possible motion trajectory as the interval between the stimulus presentations was increased. As hypothesised, in the 'Partial' control condition, in which only a section of the legs stimulus was observed, participants overall showed less of a climb in perceived 'around' motion as the ISIs increased (mean range = 57.40-64.65%) by comparison to the 'Other' and 'Self' views (mean range = 60.33-78.22%, and mean range = 49.25-72.53%, respectively, $F_{(6,174)} = 3.371$, $p = .004$).

A significant interaction between group and ISI ($F_{(3, 87)} = 2.993$, $p = .035$) revealed that normal-bodied controls were more likely to increase in their biologically plausible 'around' perceptions as ISIs increase (mean range = 54.11-77.89%), whereas the amputees' perception was not as strongly modulated with ISI (mean range = 57.21-65.71%). Across ISIs, normal-bodied controls were found to perceive the anatomically plausible 'around' motion more than amputees, but this was dependent on the body view ($F_{(2, 58)} = 3.216$, $p = .047$). Specifically, the controls perceived the physically possible more than amputees when observing the legs of another (amputees: $M = 67.13\%$, $SD = 4.60\%$; controls: $M = 73.44\%$, $SD = 3.91\%$) or the self (amputees: $M = 56.25\%$, $SD = 6.09\%$; controls: $M = 68.58\%$, $SD = 5.17\%$), but when only a part of the legs was observed, amputees perceived the 'around' motion path slightly more than the controls (amputees: $M = 62.02\%$, $SD = 4.52\%$; controls: $M = 59.12\%$, $SD = 3.84\%$).

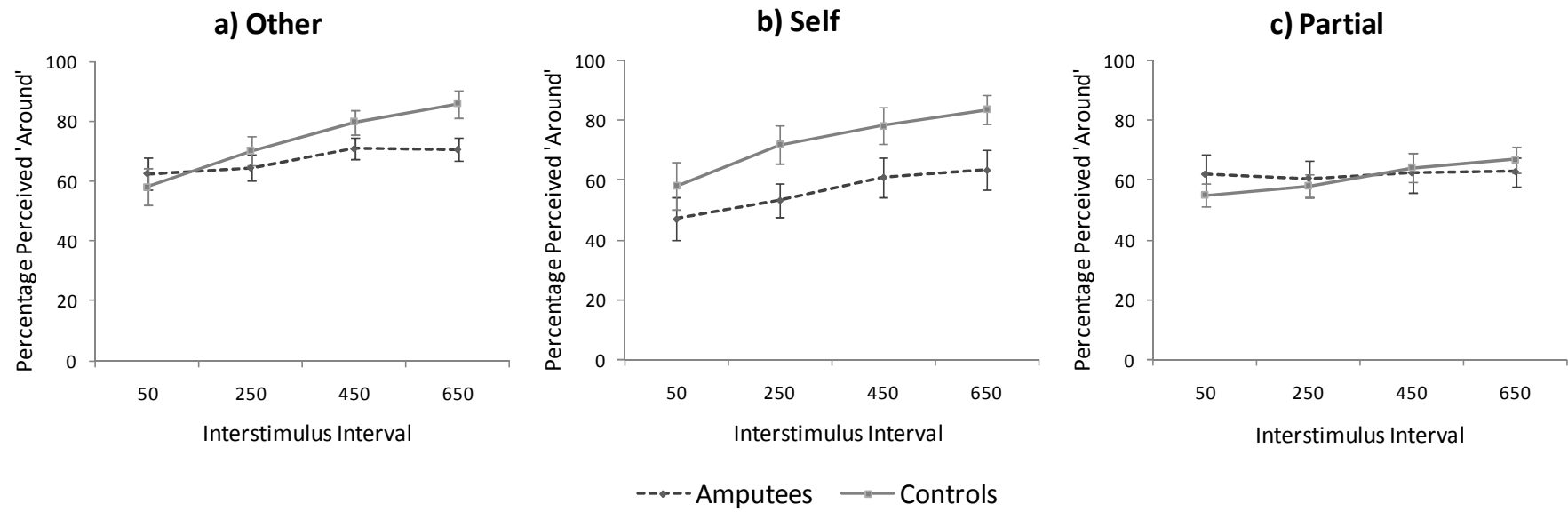


Figure 3: Mean percentage of 'around' path perceptions of apparent motion at increasing levels of ISIs for amputees and normal-bodied controls.

Overall there was no significant main effect of group ($F_{(1, 29)} = .835, p = .368$), or three-way interaction ($F_{(6, 174)} = .237, p = .964$), but there was a significant main effect of view ($F_{(2, 58)} = 5.819, p = .005$). This indicates that, across both groups, participants report seeing the biologically possible 'around' motion more in the 'Other' ($M = 70.79\%$, $SD = 16.61\%$) condition than in the 'Self' ($M = 63.41\%$, $SD = 22.45\%$; $t_{(30)} = 2.976, p = .006$) or 'Partial' condition ($M = 60.33\%$, $SD = 16.09\%$; $t_{(30)} = 3.244, p = .003$). There was no significant difference across participants and ISIs between the 'Self' and 'Partial' views ($t_{(30)} = .882, p = .385$).

Experiment 2 aimed to investigate whether amputees, all with phantom limb sensations, showed an increase in perceiving the anatomically possible route of motion as the ISI was increased. Findings by Funk *et al.* (2005) proposed that merely possessing phantom limb sensations was indicative of an intact body schema, and as such the amputees here should have shown a similar pattern of results to the general population. However, the results revealed that although both amputees and controls showed a gradual increase in perceiving the biologically plausible motion path as the ISIs were increased, this increase was significantly steeper in the control group. The amputees may in fact have had the tendency to see the limbs as moving through each other via the shortest possible trajectory more often than control participants because they had the ability to move their phantom limbs through the intact limbs and other objects.

Although in this experiment the normal-bodied participants reported perception of the biomechanically possible movement more than the amputees, this was only true of the leg conditions, 'Self' and 'Other', but not of the control 'Partial' condition where only a section of the limbs was visible. In this condition there was no difference between the two groups, indicating the likelihood that neither amputees nor controls mapped a biological body schema onto the stimuli (Chatterjee *et al.*, 1996), as the legs seemed to have failed to be perceived as moving, or even as legs at all. Many participants reported after the testing session that in the 'Partial' condition they were "just guessing" or that the stimuli "didn't even look like they were moving". This comes in contrast to Experiment 1, in which the 'Partial' condition was presented only after the other stimulus views, and did not produce a significantly different pattern of results to the other view conditions. These amputees were not systematically questioned about the solidity and mobility of their phantom limbs.

4. Experiment 3

In Experiment 3 an additional 'Arms' condition was added to determine if the change to perception in amputees was limited to the body part that was amputated, or whether the amputees merely had a problem independent to the limbloss in perceiving biological motion. The 'Partial' condition was replaced with images of alternating hockey sticks to truly represent an 'Object' condition rather than merely an inferred one (Chatterjee *et al.*, 1996). Blocks with these stimuli were interspersed with the other view conditions and counterbalanced across participants. The 'Side' condition was also dropped, as it had not revealed itself theoretically or statistically different to the 'Front' condition. The 'Front' condition in Experiments 1 and 2 are referred to henceforth as 'Other'. The order of all conditions was counterbalanced and amputees were formally interviewed to assess phantom limb phenomena, such as mobility and solidity. As Funk *et al.* (2005) advocated that no phantom limb was indicative of a limbless body schema, and phantom sensations signified an intact body schema; it is possible that a phantom limb with "faulty" qualities, such as the inability to move or a non-solid consistency, would represent an abnormal body schema. As such it would be interesting to investigate the impact this might have on affected amputees' perception of apparent biological motion.

4. 1. Method

4. 1. 1. *Participants:* Sixteen individuals with one lower-limb amputation took part in this study. The participants (all male) had not participated in Experiment 2 and ranged in age from 20 to 66 years (Mean = 52.31 years; SD = 12.02). All participants had experienced phantom sensations at some point, and further characteristics of these amputees and their phantom sensations are given in Table 2. Participants were recruited through the Sussex Rehabilitation Centre in Brighton, and had previously completed a questionnaire regarding limb deficiency and phantom limb sensations. Sixteen normal-bodied control participants who had not taken part in Experiments 1 and 2 underwent this study. The control group (6 male, 10 female) ranged in age from 27 to 81 (Mean = 49.25 years; SD = 16.36). The experiment was sponsored by the Life Sciences Ethics Committee at the University of Sussex and approved by the Brighton East Research Ethics Committee of the National Health Service (see Appendix A).

Table 2: Amputation and phantom characteristics of participants.

ID, Sex and Age	Amputation details			Phantom sensations	Phantom Characteristics	
	Years since	Cause	Side and level		Solidity	Mobility
1. M, 52	10	Infection	Right, below knee	Sometimes	Ghostly	Disabled
2. M, 59	42	Trauma	Right, below knee	Sometimes	Ghostly	Disabled
3. M, 54	24	Trauma	Right, through knee	Permanent	Solid	Disabled
4. M, 57	32	Trauma	Right, below knee	Sometimes	Ghostly	Disabled
5. M, 41	23	Trauma	Left, below knee	Permanent	Ghostly	Disabled
6. M, 53	10	Trauma	Left, above knee	Sometimes	Ghostly	Disabled
7. M, 50	31	Trauma	Right, above knee	Permanent	Ghostly	Disabled
8. M, 35	14	Trauma	Right, below knee	Permanent	Solid	Mobile
9. M, 67	49	Trauma	Right, below knee	Permanent	Ghostly	Disabled
10. M, 64	47	Trauma	Left, below knee	Sometimes	Ghostly	Mobile
11. M, 49	21	Trauma	Right, above knee	Sometimes	Solid	Disabled
12. M, 61	24	Trauma	Left, above knee	Permanent	Ghostly	Disabled
13. M, 64	13	Vascular	Right, above knee	Sometimes	Solid	Disabled
14. M, 53	17	Trauma	Left, below knee	Permanent	Ghostly	Mobile
15. M, 21	4	Trauma	Right, below knee	Sometimes	Solid	Mobile
16. M, 62	34	Trauma	Right, above knee	Sometimes	Solid	Disabled

4. 1. 2. *Materials:* In the 'Arms' condition, as in the lower-limb conditions, the pairs of stimuli represented the start and finish points of limb movements, such as arms crossing and uncrossing, which could be interpreted in two ways, i.e. as one arm moving around the other or through it (see Figure 4a). The 'Object' condition was similar to the other conditions, but employed hockey sticks in place of arms or legs (see Figure 4b). The poses the hockey sticks were placed in matched the physical angles of the legs in the 'Other' condition, to control for position bias across the conditions. All remaining stimuli used were identical to those in Experiment 2.



Figure 4: Example stimuli from 'Arms' and 'Object' conditions.

4. 1. 3. *Design and Procedure:* These were identical to those of Experiment 2 with the exception that the 'Side' condition was removed, the 'Partial' condition was replaced with an 'Object' condition, and an 'Arms' condition was added. Thus, there were four conditions: 'Other', 'Self', 'Arms' and 'Object'. All conditions were counterbalanced between participants.

4. 2. Results and Discussion

The data were treated similarly to Experiments 1 and 2 and can be found plotted as a percentage perceived 'around' path in Figure 5. A repeated-measures 2 (groups) x 4 (views) x 4 (ISIs) ANOVA found a significant main effect of ISI ($F_{(3,90)} = 8.720$, $p < .001$) suggesting that across all participants and views as the interval between stimulus presentation increased so did the participants' perception of the anatomically possible 'around' motion. There was, however, no overall main effect of group ($F_{(3,30)} = 1.365$, $p = .252$). ISI also did not interact significantly with the different views ($F_{(3,90)} = 1.726$, $p = .083$) or the groups ($F_{(3,90)} = 1.468$, $p = .229$). Although the difference between the groups is not statistically significant, all four graphs in Figure 5 indicate that normal-bodied controls tend to perceive the biomechanically plausible 'around' trajectory more often than amputees and they show a more dramatic increase in percentage of perceived 'around'.

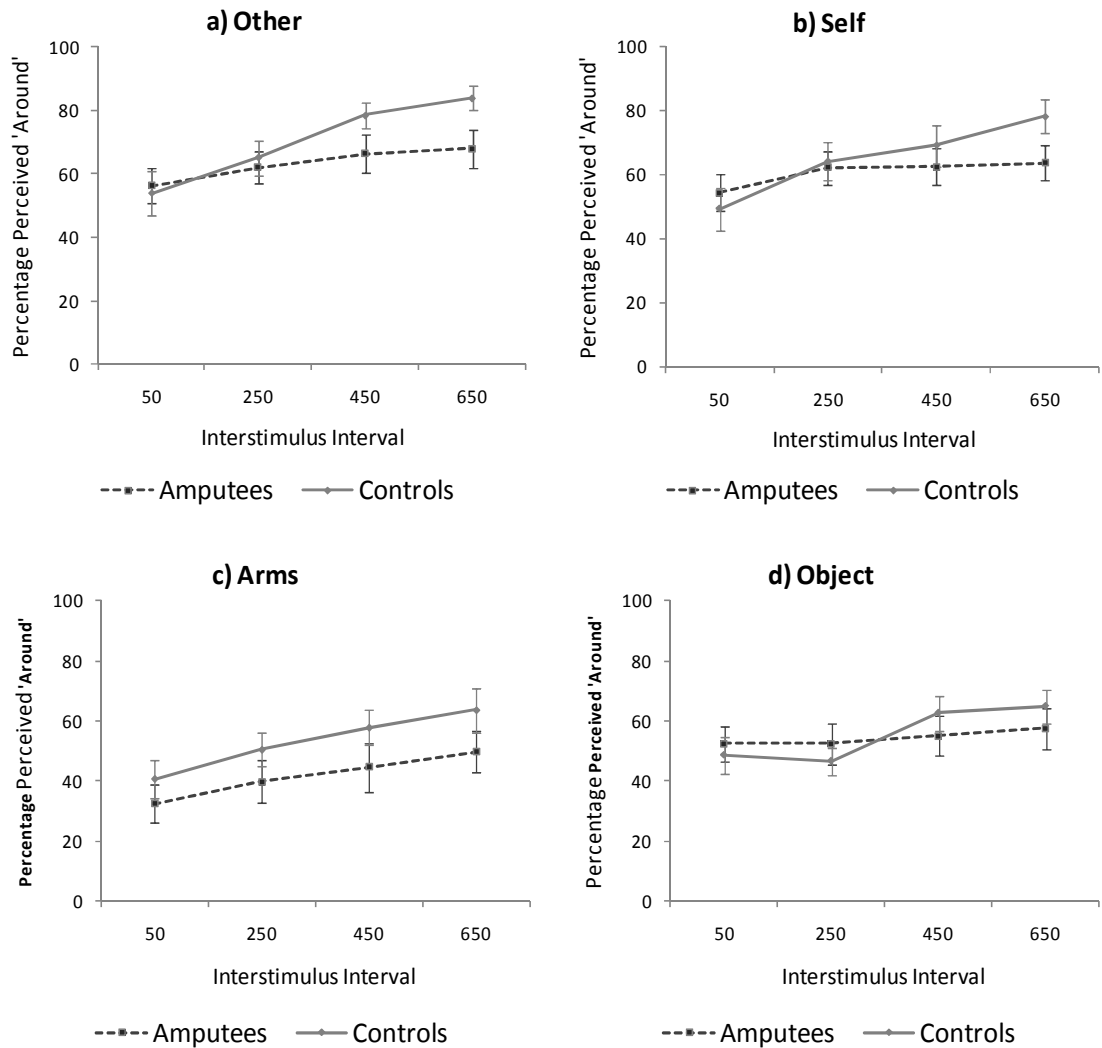


Figure 5: Mean percentage of 'around' path perceptions of apparent motion for various view conditions at increasing levels of ISIs for amputees and normal-bodied controls.

A significant main effect was revealed for view ($F_{(3,90)} = 8.720$, $p < .001$), and pairwise comparisons revealed that all conditions were significantly different from one another ($p < .05$), with the exception that there was no difference between the two leg conditions. Participants tended to perceive the biologically possible 'around' motion most in the leg conditions ('Other': $M = 66.81\%$, $SE = 2.94\%$; 'Self': $M = 62.88\%$, $SE = 3.19\%$), followed by the 'Object' condition ($M = 54.94\%$, $SE = 3.38\%$), and least in the 'Arms' condition ($M = 47.38\%$, $SE = 3.63\%$). This would suggest different processing times for the various types of stimuli, but as no view by group interaction was found ($F_{(3,90)} = .898$, $p = .446$), this cannot be said to be a process specific to lower-limb amputees. No three-way interaction was found.

Amputees were divided into two groups based on the solidity of their phantom limb sensations (solid $n = 6$; ghostly/spongy $n = 10$), and the data were averaged across the two leg conditions, 'Self' and 'Other'. A 2 (groups) \times 4 (ISIs) ANOVA revealed no significant main effects or interaction. The amputees' data were treated in a similar fashion based on the mobility characteristics of the phantom limb (fully mobile $n = 4$; impaired movement $n = 12$), and a 2 (groups) \times 4 (ISIs) ANOVA revealed no significant main effects or interaction in this case either.

In Experiment 3 the 'Partial' condition was replaced with images of hockey sticks as this was thought to be a better representative of a control condition; bodies are known to be processed differently from objects (Martin, 2007; Peelen and Downing, 2007; de Gelder *et al.*, 2010), and the stimuli were more qualitatively similar to the leg conditions (i.e. ratio of foreground to background). Although not found to be significantly different from the other view conditions, inspection of the graph in Figure 5d suggests that both amputees and controls selected at chance between the impossible and possible motion trajectories, suggesting that perhaps in this forced-choice task participants struggled to perceive the hockey sticks as moving at all.

The 'Arms' condition was introduced into Experiment 3 to investigate if the differences between amputees and controls in Experiment 2 were related specifically to their lower-limb amputation, or whether this group showed overall impaired performance that was independent of the limb amputated. As the difference between amputees and controls did not reach statistical significance for the leg or arm stimuli it could rather be suggested that the body schema remains globally intact and unchanged after amputation (Katz and Melzack, 1990; Melzack, 1990, 1992). Additionally, across the two groups all types of stimuli were found to produce different results, i.e. the biomechanically plausible path of movement was perceived to significantly different extents for leg, arm and object stimuli. This may indicate that different quantities of processing time may be required for the various stimuli. As all were presented at the same ISIs the result of this was differences in percentages of trials in which the 'around' motion path was perceived for each type of stimulus.

5. General Discussion

Overall the experiments outlined here fall in line with the early findings of Shiffrar and Freyd (1990, 1993). The normal-bodied participants' perception of apparent motion in leg and arm stimuli was constrained by the biomechanical laws that govern body movement. These

participants also showed little difference between observing the limbs of others and viewing limbs from a self-perspective, supporting the notion that these may be processed in a similar way or by the same cognitive system (Grezes and Decety, 2001; Rizzolatti *et al.*, 2001; de Vignemont and Haggard, 2008). Lower-limb amputees also tended to perceive the biologically possible more frequently as the ISI was increased, but this frequency increase was more gradual than in the general population. This suggests that limb loss may have had some impact on perception, and perhaps body schema, allowing amputees to perceive one limb as moving through the other. However, these differences were not consistently statistically significant across experiments suggesting that this change must only be moderate. The lack of perceptual differences based on the solidity or mobility of the phantom limb implicates either that changes to body schema do not necessarily impact on the perception of biological motion, or that specific qualities of the phantom limb are not indicative of a "faulty" or "abnormal" body schema.

Like the normal-bodied population, the amputees did not perceive apparent motion in the conditions where only sections of the legs were presented or where hockey sticks took the place of the limbs. This indicates that the pattern of results in the other conditions was likely due to their biological nature (Chatterjee *et al.*, 1996). The same difference between amputees and controls in steepness of the increase of perceived 'around' trajectory with ISI was found for the arm stimuli as for the leg stimuli. This would suggest that changes in the amputees' body schema and perception might occur on a more global scale. Perhaps the physical ability to move one body part through another is mapped onto the entire body schema so that it influences perception not only of the affected limb, but of other body parts as well. Research could further investigate this possibility by running the same experiment on upper-limb amputees to discover whether they show a difference in apparent motion perception of upper- and lower-limb stimuli.

Whether the phantom sensations in amputees are caused by the means of cortical reorganisation (Ramachandran and Hirstein, 1998) or as a consequence of mirror system activity (Giummarra *et al.*, 2007), these phantom sensations seem to be at least partially representative of the greater body schema (Head and Holmes, 1911-12) or maintained neuromatrix (Melzack, 1990, 1992). Perception of biological motion appears to be dependent on this to a certain degree. Although the results of the amputees are dampened relative to the normal-bodied controls, it is apparent that merely missing a limb was not enough to significantly alter perception, as both groups showed a similar pattern of results. As such, the current study brings strength to the interpretation of Funk *et al.* (2005) who suggested that it

is whether one possesses phantom limb sensations, rather than the phantom's particular qualities, that is the best indication of an intact body schema.

A dichotomy proposed by Carruthers (2008) to explain body schema suggested a difference between an *online* body representation that is constantly being updated based on the current state of the body, and an *offline* body representation which is respectively constant in representing the body's normal state. Accordingly, phantom limb sensations come about as a consequence of the brain's failure to update the body's offline element of the body schema (Berlucchi and Aglioti, 2010), i.e. the body cannot carry out actions with the missing limb, but it is still proprioceptively perceived. Hence, despite the plasticity apparent in cortical reorganisation post-amputation (Yang *et al.*, 1994; Flor *et al.*, 1995) some elements of the brain may always remain hard-wired and stable (Melzack, 1990, 1992). To further investigate this it would be of particular interest to test amputees with no phantom sensations on the apparent biological motion task. If phantom sensations are indicative of an intact body schema, phantom-less amputees should show no bias in perceiving the short or long motion path as the interval between stimuli presentation is increased. However, it is still unclear *why* such an amputee would not experience phantom sensations. It could be argued that because amputees once possessed the missing limb, an underlying neurosignature might still be present, but perhaps dormant or active at sub-threshold levels. If this were the case, amputees may show a similar pattern of results to the general population despite not experiencing phantom limb sensations.

A recent investigation employed the apparent biological motion paradigm to examine whether body schema can be modified (Moseley and Brugger, 2009). Moseley and Brugger (2009) discovered that when training amputees with intact body schemas to perform phantom wrist movements that defy normal biomechanical constraints, considerable changes were made to the body schema. The participants who successfully learnt to produce the impossible movement with their phantom arm perceived the short anatomically impossible movement path of biological motion, but only for images that portrayed apparent motion of the arm equivalent to the amputated side. Therefore, it seems that mechanisms that are purely internal have the capacity to alter body schema with no sensory or visual feedback (Moseley and Brugger, 2009). But what does this mean for the role of the mirror system in biological motion perception and phantom limb sensations? Moseley and Brugger (2009) proposed that their participants were probably mentally generating visual images of the initial and outcome states of the wrist in order to imagine what the movement would look like, and in doing so modified the internal motion plan. Research has suggested that the unified system

responsible for matching action execution and action observation is also involved in the imagination of actions (Gerardin *et al.*, 2000; Umiltà *et al.*, 2001; Keyser and Gazzola, 2006). In fact, the time it takes to consciously imagine an action is highly correlated with the time course of executing that action (Decety and Jeannerod, 1995; Jeannerod and Decety, 1995), and in patients with parietal lesions this temporal mapping is impaired (Sirigu *et al.*, 1996). It is feasible that this mirror system is employed to recall previously executed and observed actions in this motion imagery task, and perhaps it is precisely this system that is used to modify the internal body schema.

In summary, the present investigation showed that amputees and normal-bodied control participants displayed a similar pattern of results in the perception of apparent biological motion but that this pattern was more discreet in amputees. Both groups showed a gradual increase in perceiving the biomechanically plausible trajectory of motion as the interval between stimulus presentations was progressively increased. Differences in this pattern were not found based on specific phantom limb phenomena or the view from which the limbs were observed. Similarly, it seems that the same system is probably used to process leg and arm stimuli, but that this might occur at different rates for the different types of stimulus. It is conceivable that phantom limb sensations occur immediately after amputation due to either a remembered neurosignature (Melzack, 1990) or due to cortical remapping of the primary somatosensory cortex (Ramachandran and Hirstein, 1998), but that the body schema is maintained intact by a so-called 'mirror system' that matches observed actions to previously executed actions.

Paper 4

Comparing tactile spatial acuity on the face in acquired and congenital cases of lost limbs

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Limb amputation has been associated with neural remapping in the primary somatosensory cortex, but whether this phenomenon is functionally adaptive is still unclear. Studies have investigated the tactile spatial acuity of the amputated stump relative to the same location on the intact limb, and results have been divided (e.g. Vega-Bermudez and Johnson, 2002). This experiment provides the first test for the effects of cortical reorganisation on the face instead of the stump, and in doing is also the first experiment to directly compare the cutaneous sensitivity of amputees to those with congenitally malformed limbs and normal-bodied participants. Despite having used the face to control for confounding variables, such as damaged skin tissue and unequal testing site sizes, no difference was found in tactile sensitivity between the side of the face ipsilateral to the amputation site and the contralateral side of the face. Statistical differences were also not found between amputees, congenital cases and normal-bodied controls. It is possible that despite its plasticity, the primary somatosensory cortex maintains its original function, as is exemplified by referred sensations, or that the brain regions responsible for tactile acuity are not located in this part of the cortex at all. Remarkably, though, across all groups the side of the face ipsilateral to the non-dominant hand in controls (and the non-existent hand in the clinical groups) was significantly more sensitive than the side of the face ipsilateral to the dominant (or intact) hand. We propose that the face representation in the primary somatosensory cortex may be smaller on this side because the dominant hand's representation is normally larger than that of the non-dominant hand, thus making the hand more sensitive, but the face less so.

1. Introduction

The human brain holds multiple representations of the body (Head and Holmes, 1911-12). Along the post-central gyrus lies the primary somatosensory cortex which consists of a topographically organised neural map of the touch sensations received from the contralateral side of the body (Woolsey, Erickson and Gilson, 1979). In the normal body the distal extremities, such as the fingers, lips and toes, have densely-packed mechanoreceptors in the peripheral nervous system and are highly sensitive when compared to proximal regions near the torso, such as the thighs, back and shoulders. This disproportional representation results in larger regions in the "somatosensory homunculus" of the postcentral gyrus dedicated to the extremities and smaller dedicated regions for the less sensitive body parts (Penfield and Boldrey, 1937). Another general feature of this map is that areas of the body that are close to each other tend also to be close to each other in their representation within the postcentral gyrus. However, there are a few important exceptions: face and hand areas are adjacent, as are foot and genital areas.

Eliminating peripheral input by means of amputation has been shown to lead to changes in the central somatotopic map (Pons *et al.*, 1991; Yang *et al.*, 1994). Digit amputation in the raccoon and adult monkey causes an increased central representation of the neighbouring digits (e.g. Pons *et al.*, 1991; Doetsch, Stoney and Hauge, 1992), and a higher peripheral receptive field density at the amputation site (Merzenich *et al.*, 1984). Similarly, functional magnetic resonance imaging and transcranial magnetic stimulation data from human participants has suggested that the neural representation of the body parts adjacent to the deafferented region invade the cortical area that previously corresponded to the amputated body part (Cohen, Bandinelli, Findley and Hallett, 1991; Kew *et al.*, 1994; Yang *et al.*, 1994). For example, after a right hand amputation the central representations of the right forearm (adjacent on the body) and the right side of the face (adjacent along the somatosensory homunculus) expand in the cortex, and increase in sensitivity to peripheral mechanoreceptors on the skin of these body parts (Merzenich *et al.*, 1984). It has been postulated that in this very reorganisation lies the cause of phantom sensations: Proprioceptive and tactile inputs to the neighbouring body parts might reawaken the missing limb's cortical representation and maintain its essence in the form of a phantom limb (Ramachandran and Hirstein, 1998).

This begs the question as to why the primary somatosensory cortex restructures and whether this process has a functional purpose. Do the body parts adjacent to the amputation

site show enhanced performance due to their enlarged representations in the cortex? It is one opinion that the brain has evolved to undergo neuroplastic restructuring as a mechanism to rebuild the body schema so that it reflects the body's current state and in doing so preventing conflict between the input and output of somatosensory and motor areas (Ramachandran and Hirstein, 1998). Accordingly, this remapping is exhibited in the often described telescoped length and size of the phantom limb (Katz, 1992), and in the dual perceptions reported when touch to the adjacent body part is referred to the phantom limb (Ramachandran, Stewart and Rogers-Ramachandran, 1992; Halligan, Marshall, Wade, Davey and Morrison, 1993). On the other hand, Moore and Shady (2000) argue that such referred sensations are similar to the disruptive perceptual anomalies experienced in *mitempfindung*, a neural condition in which touch to one skin area causes an additional sensation at a remote body site (Muller, 1884; Schott, 1988). Moore and Shady (2000) also highlight that increase in cortical reorganisation has been repetitively associated with increased phantom *pain* sensations (Flor *et al.*, 1995; Flor *et al.*, 1998; Lotze, Flor, Grodd, Larbig and Birbaumer, 2001). As such, it is unclear why such brain neural plasticity post-amputation has evolved.

In an attempt to tackle these challenges, research has focused on the changes in tactile spatial acuity of the skin at the amputation site (Katz, 1920; Teuber, Krieger and Bender, 1949; Haber, 1955, 1958; Braune and Schady, 1993; Moore, Partner and Sedgwick, 1999; O'Boyle *et al.*, 2001; Vega-Bermudez and Johnson, 2001; Hunter, Katz and Davis, 2005, 2008). Methods of measuring cutaneous acuity assess the density of the mechanoreceptors in the skin, and hence the size of the receptive fields of cells in the somatosensory cortex. Change in tactile resolution is seen as an indirect measurement of the functional consequences of cortical reorganisation. Research has suggested that developing a skill highly, such as is seen in pianists (Ragert, Schmidt, Altenmuller and Dinse, 2004), or loss of another sense, such as in blindness (Goldreich and Kanics, 2003), can lead to an enhancement in tactile spatial acuity. Cutaneous sensitivity develops in pre-adolescence after age 9 (Bleyenheuft, Cols, Arnould and Thonnard, 2006), and positive correlations have been found between manual dysfunction associated with old age and depleted tactile resolution (Tremblay, Wong, Sanderson and Cote, 2003).

When a body part is anaesthetised not only is the tactile sensitivity of the neighbouring body parts ipsilateral to the anaesthesia improved (Bjorkman, Rosen and Lundborg, 2004), but there is also significantly better acuity interhemispherically on the homologous body part on the contralateral side (Werhahn, Mortensen, Van Boven, Zeuner and Cohen, 2002). People also experience explicit perceptual changes. When asked to draw an

image of the perceptual experience of their lips whilst the hand was under anaesthetic deafferentation, participants portrayed feeling that their lips were significantly larger than their actual size (Gandevia and Phegan, 1999). The authors suggested that inhibitory cortical connections between the hand and mouth representations were temporarily suppressed and consequently the lip region activity increased (Gandevia and Phegan, 1999). Early investigations of tactile spatial acuity in amputees showed lower thresholds in discriminating between two tactile points for the stump of above knee amputees when compared to the same region contralaterally on the intact limb (Teuber *et al.*, 1949), thus indicating heightened cutaneous sensitivity. Furthermore, the two-point discrimination threshold in upper-limb amputees was significantly lower on the stumps of amputees with telescoped phantom limbs than those with phantom phenomena that resemble an intact limb (Haber, 1955).

Would altered levels of tactile acuity also be found in congenital cases of limb deficiency? If cortical reorganisation leads to phantom sensations and enhanced tactile acuity, and amputation leads to cortical reorganisation, would those born with a missing limb even experience phantom sensations? It was once thought that prolonged kinaesthetic and sensory input from an embodied limb were necessary for a fully formulated body schema to develop in the brain (Simmel, 1962), and therefore congenital cases of phantom limb sensations could not exist (Simmel, 1959). However, Price (2006) listed 59 cases of congenital phantom limbs reported in the literature between the years 1836 and 2000, and Melzack, Israel, Lacroix and Schultz (1997) reported a 20% incidence of phantom sensations in congenital cases of limb malformation. Moreover, Melzack *et al.* (1997) pointed to two cases described by Simmel (1961) which hint at phantom sensations, and suggested that the idea of congenital phantoms was previously rejected because there was no conceptual framework for them.

Aiming to find an encapsulating theory that incorporated all misunderstood congenital and acquired phantom phenomena into an integrated body schema, Price (2006) introduced what he termed the four-part hypothesis for the developmental origins of the body image. To address body schema issues of congenital phantoms he put forward that a) the original neural representation of the body in the cortex is based on sensory and proprioceptive inputs, which b) originate in utero as a result of spontaneous muscle activity; c) transcommisural cross-cortical connections between homologous regions in the two hemispheres form a centralised representation of the body (probably in the posterior parietal cortex) by which intermanual referrals cause the phantom limb to mirror the intact contralateral limb, and d) this body schema is consolidated by means of visual input and mirror system activity, as well as sensory input and prosthesis use.

It is clear that both genes and the environment play a role in determining whether or not a phantom limb is experienced, because otherwise 100% of people born with a malformed limb would either experience a phantom or not experience one (Melzack *et al.*, 1997). Although individuals with congenital phantoms do not usually explicitly report referred sensations, as are often described by amputees and suggested to reflect cortical reorganisation (Ramachandran *et al.*, 1992; Halligan *et al.*, 1993; Halligan, Marshall and Wade, 1994; Ramachandran and Hirstein, 1998), it is possible that their face and stump do contain an element of an arm representation at sub-threshold levels. Wilson, Swinyard and Wilson (1962) compared the cutaneous resolution on the stump and homologous contralateral body part in people with congenitally missing limbs with the equivalent sites in blind participants and normal-bodied normal-sighted controls. Results found better two-point discrimination for the stump than for the intact limb, and those with a missing limb showed increased sensitivity overall when compared to both control groups. The authors suggested that the general reduction in somatosensory input overall may affect neural activity bilaterally (Wilson *et al.*, 1962).

Regardless of the cause of limb absence, early tests of two-point discrimination all seemed to suggest that merely missing a body part should enhance the tactile spatial acuity of the adjacent skin areas (Katz, 1920; Teuber *et al.*, 1949; Haber, 1955, 1958; Wilson *et al.*, 1962). However, recent studies have failed to replicate these findings (Braune and Schady, 1993; Moore and Schady, 2000; Vega-Bermudez and Johnson, 2002) or show a link between tactile sensitivity and cortical neural plasticity in amputees (Flor *et al.*, 1998; Grusser *et al.*, 2001). Hunter *et al.* (2005) found an increase in two-point discrimination sensitivity on scar tissue, but not on other areas of the stump, and this was consistently found three years later (Hunter *et al.*, 2008). Measurements of tactile acuity in the normal-bodied population have indicated the importance of selective attention in tests of spatial acuity: When participants attended only to the upper region of the arm, spatial acuity was superior to when attention was spread across the whole limb (Moore *et al.*, 1999; O'Boyle *et al.*, 2001). Moore *et al.* (1999) argued that as attention is inherently focused on a smaller area of skin in amputees, it is inevitable that they would show heightened performance on the amputated side. Higher levels of tactile acuity previously reported in amputees may simply have been the product of a selective attentional process or of testing particularly sensitive stump skin resulting from skin grafts and scar tissue.

To overcome the confounds presented by the stump's smaller surface area and damaged tissue sensitivity, the current experiment investigates the tactile spatial acuity on the

face which takes up the same amount of skin on both sides of the body, in both amputees and control participants, and this skin should not show altered tissue surface as a result of the amputation. Only one study to date has tested cutaneous acuity on the faces of upper-limb amputees. Grusser *et al.* (2001) conducted tests of two-point discrimination as well as measuring the thermal and electric thresholds of the facial skin at the corners of the lips, but did not find improved tactile sensitivity on the side ipsilateral to the amputation site relative to the contralateral side. However, this study did not investigate whether their tactile resolution was globally better than in normal-bodied controls, as would be implied by the findings of Wilson *et al.* (1962), and tactile spatial acuity in congenital cases of limb malformation was not addressed.

The aim of the study described here is to assess the tactile spatial acuity of the face on the side ipsilateral to the amputation site of upper-limb amputees relative to the contralateral side of the face, and to evaluate this difference in sensitivity with regards to that of normal-bodied controls. This will also be the first direct comparison of cutaneous sensitivity between individuals with acquired amputation and those with congenital limb deficiency. It is hypothesised that if cortical reorganisation functionally manifests itself in the tactile spatial acuity of the skin in the neighbouring cortical regions, then the skin on the face on the side ipsilateral to the amputation site should be significantly more sensitive than the homologous skin on the contralateral side of the face. Moreover, if reduced somatosensory input overall is associated with increased neural activity bilaterally, both amputees and congenital cases of limb malformation should have significantly improved cutaneous spatial resolution relative to normal-bodied controls.

2. Methods

2. 1. Participants

Fourteen individuals with only one missing upper-limb took part in this study of which one was excluded because his amputation was caused by burns to the entire body affecting the sensitivity of the skin on his face. The remaining participants consisted of two groups: acquired limb amputees and congenital cases of limb malformations. The amputees (6 male, 1 female) ranged in age from 27 to 74 years (Mean = 52.71 years; SD = 15.27). The congenital cases (3 male, 3 female) ranged in age from 26 to 80 years (Mean = 47.5 years; SD = 20.36). Further characteristics of these participants can be found in Table 1. Participants were

recruited through the Sussex Rehabilitation Centre in Brighton, and had previously completed a questionnaire regarding limb deficiency and phantom limb sensations. Twenty-nine control participants also took part and one was excluded due to damaged nerve tissue on the left side of the face which resulted from a road traffic accident many years prior to testing. The control group (15 male, 13 female) ranged in age from 21 to 81 (Mean = 49.50 years; SD = 19.27), and all reported being right-handed. The experiment was sponsored by the Life Sciences Ethics Committee at the University of Sussex and approved by the Brighton East Research Ethics Committee of the National Health Service (see Appendix A).

Table 1: Amputation and phantom limb characteristics of participants.

ID, Sex and Age	Amputation details			Phantom sensations	Handedness prior to Amputation
	Years since	Cause	Side and level		
1. M, 74	66	Trauma	Right, above elbow	Permanent	Right
2. M, 64	46	Trauma	Right, above elbow	Permanent	Right
3. M, 48	30	Trauma	Right, above elbow	Permanent	Right
4. M, 50	6	Trauma	Left, below elbow	Sometimes	Right
5. M, 45	24	Trauma	Right, above elbow	Sometimes	Right
6. M, 27	15	Trauma	Right, above elbow	Sometimes	Right
7. F, 61	55	Birth defect	Right, below elbow	Permanent	Right
8. F, 47	N/A	Congenital	Left, above elbow	Sometimes	N/A
9. F, 39	N/A	Congenital	Right, below elbow	None	N/A
10. F, 31	N/A	Congenital	Left, below elbow	None	N/A
11. M, 62	N/A	Congenital	Left, above elbow	None	N/A
12. M, 26	N/A	Congenital	Right, below elbow	None	N/A
13. M, 80	N/A	Congenital	Right, below elbow	None	N/A

2. 2. Materials

J.V.P. Domes were used to provide a quantitative measurement of the face's cutaneous spatial resolution (Johnson, Van Boven and Phillips, 1997). These are a set of eight circular plastic domes with deep rectangular grooves cut into their surface. The width and spacing of the grooves are equal in width and differ from dome to dome, starting with a 3 millimetres grating at the largest size and graduating down to a .35 millimetres grating at the smallest size (see Figure 1 for example gratings). J.V.P. Domes have reliably proven to be the most accurate tool for testing somatosensory sensitivity (Van Boven and Johnson, 1994; Vega-Bermudez and Johnson, 2002).



Figure 1: Example of J.V.P. Domes used to measure the cutaneous sensitivity of participants' faces. From left: 3 millimetre, 1 millimetre and .35 millimetre gratings.

Difference scores from the current test were correlated with questionnaire (see Appendix B) responses to the following questions to address their relatedness to 1) time since amputation, 2) phantom pain intensity, and 3) phantom pain frequency:

(1) *What was your age at the time of amputation?* Scores were calculated by adding the age reported to the year provided in the date of birth.

(2) *Please indicate the level of pain associated with the phantom limb (i.e. not the stump) at its worst.* Participants were instructed to draw a straight line through a 100 millimetre visual analogue scale in which "No Pain" labelled one extreme and "Unbearable Pain" labelled the other. The number of millimetres between zero and their dividing line was recorded as their score.

(3) *How often does / did this pain occur?* Scores of 0-8 were given for the following responses: a) Permanent, b) Several times a day, c) Once a day, d) Several times a week, e) Once a week, f) Once a fortnight, g) Once a month, and h) Less than once a month (8 = Permanent).

2. 3. Design and Procedure

Prior to testing, participants were briefed regarding the experimental procedure and allowed to familiarise themselves visually and haptically with the domes, but they remained naive to the purpose of the task. Participants confirmed they understood the difference between 'horizontal' and 'vertical'. They were also asked to close their eyes during testing to enhance their somatosensory attention and to ensure that they didn't see the grooves. A tape-measure was used to find the centre of each cheek by calculating the midpoint between the edge of the nose and the bottom of the earlobe; this point was marked by a dot with a bald-point pen. The location was marked to ensure that the same location was stimulated in each trial and was constant across participants. This point was selected because Hunter *et al.* (2003) found the cheek to be the most likely site to generate referred sensations, and thus activate the hand area of the primary somatosensory cortex. In a forced-choice task, a staircase design was implemented by which the largest dome was placed against the testing site; if the participant correctly reported the dome's orientation on two consecutive trials the grating size was decreased. A single incorrect response would lead to an increase in grating size. The test continued until there had been 12 grating size reversals, in which the last 10 were used to calculate the site's tactile acuity threshold (Wetherill and Levitt, 1965; Stevens, 1992). Each dome was placed against the skin for approximately two seconds, and care was taken so that the dome did not move laterally and give a hint as to its orientation. No feedback was given to the participants regarding correct and incorrect responses to prevent the use of spurious cues. The test was always run primarily on the right cheek followed by the left, and the order of the orientation presentation was randomly generated for each cheek.

Referred sensations were also tested for by stimulating each of the sites indicated in Figure 2 with a paintbrush. In sites where participants had hair, the back of the paintbrush was used. The participants were asked to report if the touch induced sensations in the phantom limb, and if so they were prompted to localise it. This was carried out on completion of tactile spatial acuity task in order not to raise suspicions about the aim of the test. Participants were finally thanked, debriefed and given the opportunity to ask questions.

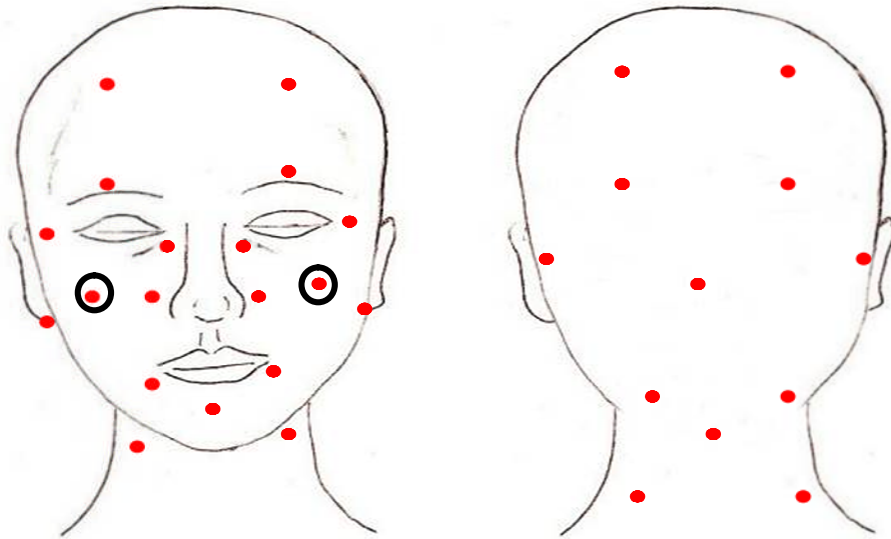


Figure 2: Sites of stimulation for examining referred sensations. Testing sites are circled.

3. Results

The measurements of the gratings on the domes for each of the last 10 dome reversals were averaged to compute a tactile spatial acuity score for each side of the face for each participant. The means of these scores across participants in each group are presented in Figure 3. The level of performance by chance was calculated to be 2.35 (SD = .37, range = 1.97-2.5) by flipping a coin for 10 sets of 10 reversals. "Heads" represented a horizontal report, and "tails" represented a vertical report.

Controls could have been matched to the clinical groups in one of two ways: a) handedness, or b) dominance. All control participants were right-handed, and within-subjects t-test revealed no significant difference in tactile spatial sensitivity between their right and left cheeks ($t_{(27)} = 1.04$, $p = .306$), suggesting that cutaneous sensitivity on the cheek was not dependent on the participants' handedness. As such, rather than randomly distributing the controls' right side and left side data to match the amputees' 69% right side amputations, and 31% left side amputations; all right side (the dominant side) data for controls were matched to the intact limb in the clinical groups, and all left side (the non-dominant side) data were matched to the amputated side.

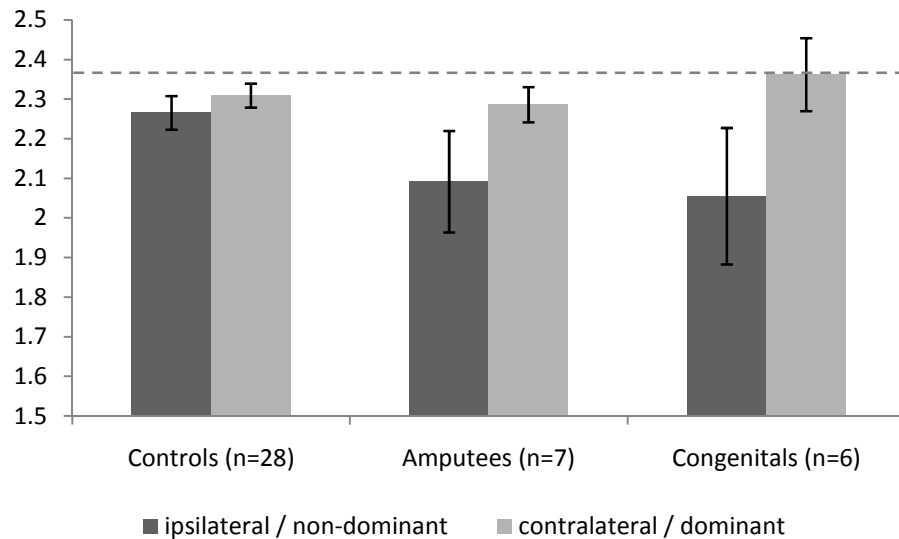


Figure 3: Average tactile spatial acuity scores for the ipsilateral and contralateral cheeks of amputees, congenital and controls. The error bars represent ± 1 standard error of the mean and the dotted line indicates chance performance.

Overall amputees ($M = 2.19$, $SE = .06$) and congenital participants ($M = 2.21$, $SE = .07$) showed higher cutaneous sensitivity than control participants ($M = 2.29$, $SE = .03$), and the ipsilateral side of the face to the amputation (amputees: $M = 2.09$, $SE = .10$; congenital: $M = 2.06$, $SE = .11$) was more sensitive than the contralateral side (amputees: $M = 2.29$, $SE = .06$; congenital: $M = 2.36$, $SE = .07$). A mixed-model 3 (group) \times 2 (side of face) ANOVA revealed a significant main effect of the side of face tested ($F_{(1,38)} = 9.74$, $p = .003$), indicating that across all participants the cheek on the side of the amputated/non-dominant limb ($M = 2.14$, $SE = .05$) showed significantly more cutaneous sensitivity than the cheek on the intact/dominant limb side ($M = 2.32$, $SE = .03$). However, no significant difference was found between the three groups ($F_{(2, 38)} = 2.30$, $p = .114$), and there was no interaction between group and side of face ($F_{(2, 38)} = 1.297$, $p = .285$). The difference in tactile spatial acuity between the contralateral and ipsilateral cheeks for the data of the non-congenital amputees was computed and correlated with questionnaire data for 'years since amputation', 'phantom pain intensity' and 'phantom pain frequency'. No relationships were found ($p > .05$).

All seven amputees experienced phantom limb sensations, and reported referred sensations when stimulated on the face with a paintbrush. The sites which caused participants to report referred sensations are indicated in Figure 4. Participants 2, 4, and 6 (in Table 1) reported referred sensation from the testing site in the centre of the cheek. Participant 2 showed very high cutaneous sensitivity on the ipsilateral cheek with a score of 1.41

millimetres, and participants 4 and 6 showed the same sensitivity on both cheeks, but reported the highest phantom pain frequencies in the group and showed referred sensations from the most points on the face. This might suggest a link between referred sensations and frequency of phantom pain.

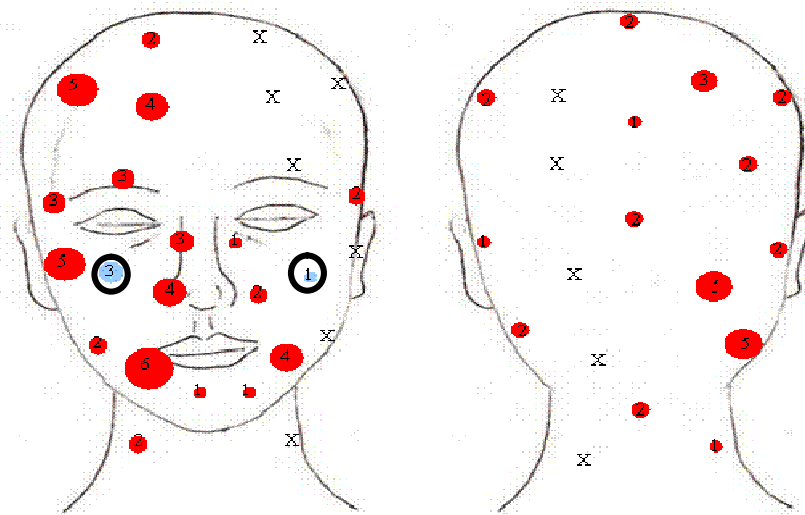


Figure 4: Stimulation sites for referred sensations. The larger the dot, the higher the incidence of referral; the number indicates the number of participants who reported experiencing referred sensations as a consequence of stimulation. In left-handed amputees the image was mirror-reversed so that the outer side of this image always represented the amputated side.

4. General Discussion

This study assessed the tactile spatial acuity on the face after a limb had been amputated or was congenitally missing. As the central representation of the face in the primary somatosensory cortex is adjacent to that of the hand (Penfield and Boldrey, 1937; Woolsey *et al.*, 1979), it was hypothesised that due to the cortical reorganisation that occurs post-amputation (Yang *et al.*, 1994) the ipsilateral side of the face would come to represent the missing hand (Halligan *et al.*, 1993), and that this would be exhibited by an increase in the face's cutaneous sensitivity (Teuber *et al.*, 1949; Haber, 1955, 1958; Wilson *et al.*, 1962). In accord with recent studies investigating such tactile sensitivity on the stump (Braune and Schady, 1993; Flor *et al.*, 1998; Moore and Schady, 2000; Grusser *et al.*, 2001; Vega-Bermudez and Johnson, 2002; Hunter *et al.*, 2005, 2008), the current test failed to demonstrate a significant difference in tactile acuity between the two sides of the face in people with a missing limb or a difference in overall sensitivity between these individuals and normal-bodied

controls. Moore *et al.* (1999) postulated that the only reason early research found differences in tactile acuity between the stump and the homologous region contralaterally (Teuber *et al.*, 1949; Haber, 1955, 1958; Wilson *et al.*, 1962) was because the participants' attention was focused on a smaller area of skin. This explanation cannot be applied to our data, because the test sites were equal in size and visual attention affects were prevented by asking participants to shut their eyes. Similarly, our testing sites were not confounded by sensitive scar tissue from the amputation surgery as was seen in other studies (Hunter *et al.*, 2005, 2008).

Vega-Bermudez and Johnson (2002) looked at the tactile sensitivity of digits adjacent to an amputated digit relative to the same digits on the other hand. They too found no difference between the two sides of the body and no difference between amputees and normal-bodied controls. As such they proposed two theories to explain why cortical reorganisation did not seem to alter cutaneous sensitivity. Firstly, they suggested that the neighbouring cortical regions may take over the "silent" cortex, but that this does not improve tactile acuity because the deafferented cortex still operates the same perceptual functions as always; it produces tactile and proprioceptive sensations, i.e. now as referred sensations, in the digits that it topographically represents, i.e. the now phantom digits. Accordingly, the function of cortical reorganisation is not to enhance the tactile spatial resolution, but rather the neural plasticity may just be an epiphenomenon of amputation explained simply by the unmasking of existing normally ineffective neural contacts in the brain (Wall, 1977). Similarly, Vega-Bermudez and Johnson's (2002) second explanation suggested that perhaps reorganisation in the primary somatosensory cortex is not relevant here. It is possible that the circuits responsible for the cutaneous resolution do not lie in cortical regions that restructure after amputation, but rather lie in more central areas of the nervous system.

The accounts put forward by Vega-Bermudez and Johnson (2002), however, do not provide an explanation as to why our experiment found the side of the face ipsilateral to the non-dominant hand in controls, and the non-existent hand in the clinical populations, to have a significantly enhanced tactile sensitivity relative to the side of the face ipsilateral to the dominant, or intact, hand. Studies of tactile spatial acuity in the general population tend to show better cutaneous resolutions for the skin of the dominant upper and lower limbs (e.g. Weinstein and Sersen, 1961), but usually no difference has been reported between the two sides of the face (Ringel and Ewanowski, 1965; Kesarwani *et al.*, 1989; Posnick, Zimbler and Grossman, 1990; Chen *et al.*, 1995; Wohlert, 1996). However, in the one instance in which a difference was found in the sensitivity of the two sides of the face (Lee and Essick, 1993), the direction of the results was similar to ours. The left non-dominant side of the face was more

sensitive for right-handed participants. As this difference was found in the same direction across all three groups in the current investigation, it is reasonable to consider that there are fewer mechanoreceptors on the face ipsilateral to the dominant hand because of the interhemispheric asymmetry of the hand representation in the sensory-motor cortical regions. The topographical representation of the hand along the central sulcus is usually larger in the left hemisphere of right-handed people (White, Lucas, Richards and Purves, 1994), and may lead to smaller or fewer receptive fields for the representation of the face in the primary somatosensory cortex on this side. It is generally believed that handedness (Annett, 1985; McManus, 1991; Annett, 1995) and cerebral asymmetry (Beaton, 1997; Corballis, 2009) are genetic, and as such should not differ between amputees and controls. This is supported by the data of our amputees. All seven of our participants were right-handed prior to amputation and only two underwent a left limb amputation; despite the change in hand dominance from right to left in five of the amputees, difference in tactile acuity on the face remained in the same direction as in the normal-bodied population. In order to investigate this further a larger sample of upper-limb amputees would be necessary.

What do the findings of the current research suggest about congenital cases of limb malformation? On first impression, it could be concluded that the similar pattern of results for both those born with only one arm and those who had lost an arm strengthens the argument that cortical reorganisation does not cause enhanced cutaneous acuity, because of the lack of amputation and therefore the lack in related cortical reorganisation experienced by the congenital cases (Simmel, 1959, 1961). However, when considering modern theories all suggesting that congenital phantom limbs must, at least in part, be caused by inter-hemispheric and environmental cues (Melzack *et al.*, 1997; Price, 2006; Giummarra, Gibson, Georgiou-Karistianis and Bradshaw, 2007; Fitzgibbon, Giummarra, Georgiou-Karistianis, Enticott and Bradshaw, 2010), it would be wrong to assume that there would necessarily be a difference in the result of these two groups because multiple factors may play a role in phantom limb phenomena, such as commissural connections across the corpus callosum, mirror system activity and prenatal development.

Thus before dismissing a link between somatosensory cortical reorganisation and enhanced tactile acuity due to the lack of a statistically significant difference between the groups in tactile acuity, methodological issues must be addressed. The centre of the cheek was selected as the testing site because Hunter *et al.* (2003) found it to be the most likely to induce referred sensation to the phantom, and topographical maps produced in other literature have suggested the same (Halligan *et al.*, 1993; Ramachandran *et al.*, 1992). Despite

this, our test for referred sensations found that only three amputees experienced referred sensations from the centre of the cheek. However, nearly all had referred sensations from the lower corners of the lips. Moreover, in testing the normal-bodied population Patel, Essick and Kelly, (1997) found that gratings of 3 millimetres and less to test for tactile acuity on the face were only viable for testing regions densely packed with mechanoreceptors, namely areas on or near the lips. They warn that coarser gratings are necessary for testing other sites on the face in order to avoid a false-positive diagnosis of sensory impairment. As the level of tactile acuity across all participants in this study was relatively close to chance, it is possible that the gratings used in this study were too fine for the skin region we were testing. The pattern of our results falls in line with those hypothesised, and testing a site nearer the lip, using larger gratings or testing more patients might have led these results to reach statistical significance.

Although most of the recent literature has failed to find a difference in the tactile acuity of the two sides of the body when a limb is absent (Braune and Schady, 1993; Flor *et al.*, 1998; Moore and Schady, 2000; Grusser *et al.*, 2001; Vega-Bermudez and Johnson, 2002; Hunter *et al.*, 2005, 2008), the current experiment was carried out to control for the confounding variables associated with testing the cutaneous resolution of the skin on the stump, i.e. extra-sensitive scar tissue and disproportionate testing site sizes. Despite this, no difference was found between the two sides of the face in individuals with one arm by comparison to normal-bodied controls. It is possible that this is because the primary somatosensory cortex maintains its original perceptual function, or because the brain regions responsible for tactile acuity are not based in the primary somatosensory cortex (Vega-Bermudez and Johnson, 2002). However, our pattern of results does show the contralateral side of the face to the dominant/intact hand to be more sensitive than the other side of the face across all participants. This might be because the dominant hand has been shown to have a larger topographical representation in the primary somatosensory cortex (e.g. White *et al.*, 1994) which could shrink the adjacent face representation. But it is also possible that this difference was driven by the data from participants with missing arms, especially as no difference has normally been found in the tactile sensitivity of the two sides of the face of the general population (e.g. Chen *et al.*, 1995).

These findings impose no doubt as to whether neuroplastic changes occur in the primary somatosensory cortex after amputation as has been demonstrated by single-cell recordings in animals (Merzenich *et al.*, 1984; Pons *et al.*, 1991; Doetsch *et al.*, 1992), as well as functional neuroimaging and transcranial stimulation studies in humans (Cohen *et al.*, 1991; Kew *et al.*, 1994; Yang *et al.*, 1994), but rather furthers the question as to why such cortical

reorganisation takes place. Whether or not inferring from this data that tactile acuity is enhanced in the facial skin of people with only one arm, new questions arise. For example, if the skin on the face is more sensitive on the ipsilateral side to the missing limb, why hasn't the skin on the stump also been shown to have greater cutaneous acuity? On the other hand, if cortical reorganisation does not lead to better tactile acuity then why *does* it occur? The neural plasticity after amputation has been associated with referred sensations (Ramachandran *et al.*, 1992; Halligan *et al.*, 1993), telescoping (Katz, 1992) and pain sensations (Flor *et al.*, 1995; Lotze *et al.*, 2001), all of which don't seem to be explicitly adaptive qualities. Thus, the current research has contributed to the pool of knowledge regarding the consequences of limb amputation and their relation to primary somatosensory cortical reorganisation, and puts further demand on the pursuit of understanding *why* cortical reorganisation occurs after amputation.

Paper 5

Developing an objective measure of referred tactile sensations in amputees

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Referred tactile sensations from the face and amputated stump into the phantom hand are frequently reported in research about amputees. However, most studies have relied on self-reports and correlational neuroimaging techniques to provide evidence for this phenomenon. The current experiment was the first that aimed to develop an objective standardised paradigm to empirically test reports of such dual percepts. In a one-handed adaptation of Driver and Spence' (1998) tactile-visual cueing paradigm, we aimed to determine if a tactile cue presented to the face and referred to the phantom hand could prime the location of a visual target on a rubber hand positioned in the space occupied by the phantom. Experiment 1 proved the one-handed version of the crossmodal cuing paradigm to be successful in a normal-bodied sample; spatial discrimination decisions were faster when the cue and target were presented on the same side of the hand. However, in Experiment 2 the cuing paradigm was found to be so robust that despite the distance between the rubber hand and the face, the real touch to the face had a greater cuing influence on the target than its referred touch sensation in the phantom. As such an objective method for measuring referred tactile sensations is still needed. We recommend following in the footsteps of Ehrsson *et al.* (2008) and trying to test this with the rubber hand illusion.

1. Introduction

Despite the physical change that occurs to the body following amputation, over 95% of patients describe a ghostly phantom sensation as though the limb is still physically present and can be used in much a similar way to a normal limb (Melzack, 1992). Moreover, approximately 68% of amputees report a referral of sensations as touch to the body parts adjacent to the amputation site elicit the feeling of touch in the extremities of the phantom (Kern, Martin, Scheicher and Muller, 2006). For example, some upper-limb amputees have reported a feeling of their phantom fingers being touched when their face was tactily stimulated on the ipsilateral side by another person (Ramachandran, Rogers-Ramachandran and Stewart, 1992a; Ramachandran, Stewart and Rogers-Ramachandran, 1992b). The individual regions of the phantom, e.g. thumb, palm and digits, are often represented as a topographically organised map of trigger zones on the referring body parts, i.e. the face and stump (Halligan, Marshall, Wade, Davey and Morrison, 1993). This form of referred sensations is even experienced in the opposite direction, i.e. touch to the hand and forehead after the removal of tumours from the cheek sometimes evoke sensations in the deafferented part of the face (Clarke, Regli, Janzer, Assal and deTribolet, 1996), and referred sensations can be reversed after transplantation (e.g. Farne, Roy, Giraux, Dubernard and Sirigu, 2002). Referred sensations have also been reported in chronic pain patients (Katz and Melzack, 1987), stroke patients (Turton and Butler, 2001), spinal cord injury patients (Soler *et al.*, 2010) and patients with various brain lesions leading to hemiparesis (Sathian, 2000). Further research has indicated that with time the acute topographic mapping of trigger zones may become disorganised (Halligan, Marshall and Wade, 1994), and that the distribution of the digits' representations may alter so that the most proficient digit has a larger trigger zone area than the others (Ramachandran and Hirstein, 1998).

Insight into the source of such perceptual phantom phenomena in amputees can be gained from the reorganisation of the neural inputs from the body that occurs in the brain subsequent to amputation. After amputation of a limb the newly 'vacated' region of the primary somatosensory cortex that formerly responded to that limb becomes 'invaded' by neighbouring areas of the brain (Merzenich *et al.*, 1984; Cohen, Bandinelli, Findley and Hallett, 1991; Pons *et al.*, 1991; Yang *et al.*, 1994), either by means of the removal of pre-existing inhibitory neural connections or through the sprouting of new ones (see Ramachandran and Hirstein, 1998). Generally, touch to one side of the body is mapped onto the primary somatosensory cortex along the contralateral post-central gyrus, and in this map parts of the

body that are near each other on the physical surface tend to be represented side by side in the somatosensory cortex (Penfield and Boldrey, 1937). There are only a few exceptions to this, namely the close proximity of the face to the hand and the genitals to the foot (Penfield and Boldrey, 1937; Farah, 1998). The reorganisation that occurs following amputation means that touch to the stump and face (in upper-limb amputees) or genitals (in lower-limb amputees) will lead to primary somatosensory hand or foot activity, respectively. This is in turn interpreted by higher brain regions as touch to the phantom limb. Ramachandran and Hirstein (1998) argued that it is this very reorganisation that is the cause of the general phantom limb existence.

Most research investigating the phenomenon of referred sensations has relied on self-reports about the patients' personal experiences when being stroked with a cotton bud, brush or finger, pricked with a pin, needle, von Frey hairs or an algesiometer, touched with a blunt pencil, a 40°C heated thermode or an ice pack/cube or stimulated with a vibrating 128/256-Hz tuning fork, weighted Semmes-Weinstein monofilaments or pneumatic pressure stimulator (Katz and Melzack, 1987; Ramachandran *et al.*, 1992a; Ramachandran *et al.*, 1992b; Halligan *et al.*, 1993; Halligan *et al.*, 1994; Doetsch, 1997; Ramachandran and Hirstein, 1998; Sathian, 2000; Turton and Butler, 2001; Kern *et al.*, 2006; Soler *et al.*, 2010). These reports are usually obtained verbally or at times marked on a printed diagram of the body (e.g. Soler *et al.*, 2010). Authors often report that the participants are surprised by the dual percept (e.g. Ramachandran and Hirstein, 1998), unless they'd noticed the sensations themselves before (Halligan *et al.*, 1993), or that extra care was taken to prevent the participant from knowing the purpose of the stimulation test (e.g. Knecht *et al.*, 1996; Grusser *et al.*, 2001). However, the authenticity of referred sensations has never been directly experimentally tested. Although the significant body of research on the topic suggests that these personal descriptions are reproducible, a more objective means for empirically testing the occurrence of referred sensations in amputees would shed further light on the cause and characteristics of these experiences.

Although still employing the same methods, functional neuroimaging and transcranial stimulation studies have aimed to uncover the neural correlates of such referred phantom sensations (Elbert *et al.*, 1994; Knecht *et al.*, 1996; Pascual-Leone, Peris, Tormos, Pascual and Catala, 1996; Borsook *et al.*, 1998; Davis *et al.*, 1998; Montoya *et al.*, 1998; Grusser *et al.*, 2001; Grusser *et al.*, 2004). A few studies have shown that referred sensations induced with a painful stimulus, but not non-painful referred sensations, are associated with reorganisation in the primary somatosensory cortex (Knecht *et al.*, 1996; Montoya *et al.*, 1998; Grusser *et al.*,

2001), but the authors attribute this to the correlation between general phantom limb pain and post-amputation brain plasticity. Much of the neuromagnetic imaging research conducted in amputees illustrated that general increase in phantom *pain* is associated with greater cortical reorganisation (Flor *et al.*, 1995; Lotze, Flor, Grodd, Larbig and Birbaumer, 2001; Lacoux, Crombie and Macrae, 2002), and thus this may not be specific to referred sensations phenomena. Grusser *et al.* (2004), however, found a significant enlargement of the mouth representation in the primary somatosensory cortex for non-painful referred sensations, and another study showed increased blood oxygenation level dependent signals in response to non-painful referred sensations in the post-central gyrus, supplementary motor area and posterior cingulate gyrus (Borsook *et al.*, 1998).

However, Grusser *et al.* (2004) and Borsook *et al.* (1998) also introduced a finding that cannot directly be explained by Ramachandran *et al.*'s (1992a; 1992b; Ramachandran and Hirstein, 1998) theory. These studies showed that tactile stimulation of the foot produced referred sensations in the phantom arm of upper-limb amputees. As these body parts are not represented in close proximity to each other in the primary somatosensory cortex (Penfield and Boldrey, 1937), it is unclear why such referral of sensations would be brought about after amputation. Moreover, there was no significant difference in the location of the toe representations in the cortex ipsilateral to the amputation site when compared to the contralateral side of the cortex (Grusser *et al.*, 2004), suggesting that other cortical structures may be responsible for referred phantom sensations, such as the thalamus (Borsook *et al.*, 1998; Grusser *et al.*, 2004) or the secondary somatosensory cortex, posterior parietal cortex and prefrontal cortex (Grusser *et al.*, 2004). In support of this notion, using magnetic source imaging, Elbert *et al.* (1994) failed to find a relationship between cortical reorganisation and facial remapping. They proposed that although cortical reorganisation may be necessary to induce referred sensations, it is not sufficient in and of itself to explain the cause of such phenomena. Thus, not only have neurostimulation and magnetic resonance imaging studies produced contradictory findings and conclusions, they are merely correlational in nature and do not clarify whether it is in fact the reorganisation that triggers the referred sensations, or whether other factors or brain regions also play a causal role.

In behavioural methodologies, Braun *et al.* (2005) point to the subjective problems of testing for dual percepts and mislocalised sensations manually. They discuss the human errors that may come about, such as difficulties involved in maintaining spatial precision, constant speed, similar positioning angles and preventing horizontal movement. As such they developed an automated testing device which could deliver faint tactile stimuli with greater

sensitivity than manual testing and this device has proven to produce a sharper gradient of responses (Braun *et al.*, 2005). Although their apparatus provides resolve for some testing technique issues which ought to be considered, no solution is suggested for the subjective bias that is inevitable in self-report data. When studying referred sensations in amputees, researchers rely solely on personal accounts of the participants' experiences, and often generalised inferences are made on the basis of these when interpreting functional neuroimaging data (e.g. Elbert *et al.*, 1994; Knecht *et al.*, 1996; Borsook *et al.*, 1998; Montoya *et al.*, 1998; Grusser *et al.*, 2001; Grusser *et al.*, 2004). Thus, it is vital that a method is found for testing the reliability and viability of referred sensations that not only controls for experimenter bias and skill, but also for participant subjectivity, expectation and opinion.

A recent experimental behavioural study employed the rubber hand illusion to indirectly investigate the referred sensations phenomenon (Ehrsson *et al.*, 2008). In the normal-bodied population the rubber hand illusion involves stroking a dummy hand concurrently with the participant's own hand while it is hidden from sight; with time the rubber hand becomes embodied by the participants as they feel ownership of the dummy hand. Participants tend to then estimate the location of their own occluded hand to be physically closer to the location of the rubber hand (Botvinick and Cohen, 1998). Ehrsson *et al.* (2008) "were dubious whether this illusion could be elicited in amputees" (p. 3444) because normally for the illusion to be effective the real hand and rubber hand must be stimulated in precisely the same location. Nonetheless, their findings showed that the referred sensations from touch to the end of the stump were sufficient to match the touch to the hand and elicit the rubber hand illusion in amputees. Significant differences were found in drift of perceived phantom location toward the rubber hand between stroking the rubber hand and stump synchronously and stroking these asynchronously. Similarly, skin conductance in the stump was affected when the rubber hand appeared to be under physical threat. The success of these tasks provides indirect experimental evidence for referred sensations as without these sensations the illusion should not have been perceived at all.

The current study aims to develop an experimental paradigm that directly and empirically tests self-report of referred sensations. This experiment is designed to expand on the findings of Ehrsson *et al.* (2008) by investigating the remapping of the hand onto the face rather than the stump. As the stump is physically adjacent to the site of amputation, the skin that's stretched and folded over the the operation site formerly represented sections of the limb that are now phantom (Haber, 1955). This skin also often shows heightened sensitivity due to skin grafts and scar tissue (Hunter, Katz and Davis, 2005, 2008). The study will also

extend findings into the cross-modal field by investigating the interaction between vision and touch in the referred sensation of amputees. Unlike other literature that has shown contradicting findings as to whether these sensations are modality-specific, i.e. a cold stimulus producing a cold referred sensation (e.g. Ramachandran *et al.*, 1992b, versus Halligan *et al.*, 1993), the objective of this investigation is to determine if a tactile referred sensation can influence the perception of a visual stimulus.

The experiment proposed here is based on orthogonal cuing methodologies put forward to test spatial selective attention by Driver and Spence (1998a, 1998b, 2000). In an example of a standard attentional cuing experiment participants hold a cube in each of their hands at approximately 20° from their midline; each cube contains two tactile stimulators and two light emitting diodes with one of each held by the index finger pad and one of each held by the thumb pad (see Figure 1). On an experimental trial a task-irrelevant tactile cue is presented to both stimulators of one hand or the other 100-300 milliseconds prior to the flicker of a single visual target on either the top or bottom of the left or right hand. When the tactile cue is presented on the same hand as the visual target, elevation discrimination decisions, i.e. judgments as to whether the light came from above or below, are faster and more accurate. This suggests that the attention drawn towards the cue enhances localisation skills of target stimuli in the cued space, and thus response to a target in that space is improved.

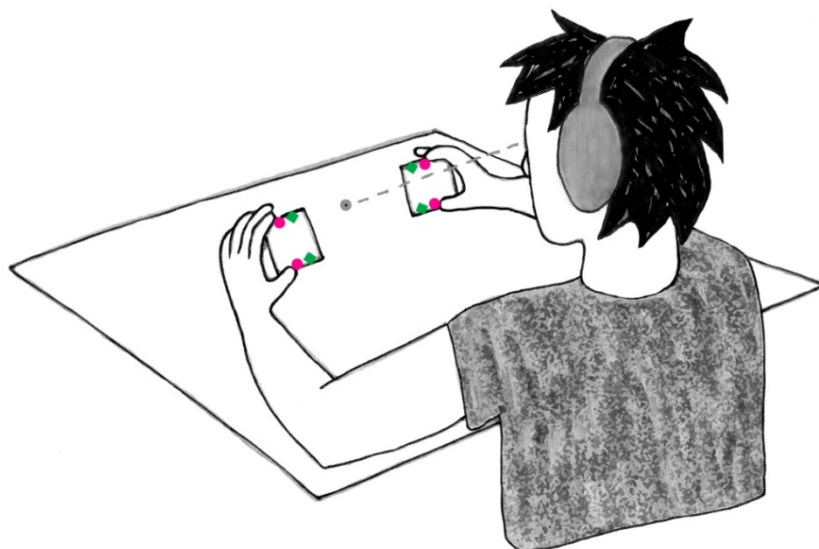


Figure 1: The set-up of an orthogonal cuing experiment (adapted from Soto-Faraco et al., 2004). Pink circles symbolise vibrotactile stimulators and green squares symbolise light emitting diodes. Dot in centre of table acts as visual fixation and headphones playing white noise are worn to prevent auditory signals from the vibrotactile stimulators.

In a one-handed adaptation of the crossmodal attention task for amputees, participants in the current study were presented with light emitting diodes in two locations on a rubber hand. Tappers were attached to the two regions of the face that elicited referred sensations in these locations of the phantom. On each trial amputees experienced a tactile cue to *one* of the face sites followed by the appearance of a visual target on *one* of the rubber hand sites. Participants were instructed to make speeded "right or left" spatial discrimination decisions about the location of the visual target. It was predicted that tactile cuing to one site of the face would lead to faster and more accurate spatial discrimination decisions if the visual target appeared in the corresponding location, as in the classic orthogonal cuing studies (Driver and Spence, 1998a, 1998b; Driver, 2001; Eimer and Driver, 2001; Soto-Faraco, Ronald and Spence, 2004). Such a result would suggest that the space represented in the place of the amputated hand has genuinely been remapped onto the ipsilateral face area.

2. Experiment 1

The aim of the first experiment was to pilot the adapted one-hand experiment set-up on a group of normal-bodied individuals to ensure that the modified orthogonal cuing task was valid and consistent with previous findings in the general population. Half of the participants were tested on their dominant hand and the others on their non-dominant hand in order to investigate whether there was a difference between these. As the general population do not experience referred sensations when their faces are touched, the participants were presented with both the tactile cue and the visual target on the same hand locations. The findings described by Driver and Spence (1998a, 1998b, 2000; Driver, 2001) suggested that reaction times for identifying the target location would be better when the tactile cue and visual target were presented on the same side of the hand rather than on incongruent sides of the hand.

2. 1. Method

2. 1. 1. *Participants:* Thirteen undergraduate psychology students at the University of Sussex volunteered for this task. The participants (3 male, 10 female) ranged in age from 18 to 29 years (Mean = 20.69 years; SD = 3.35). Twelve of the participants reported being right-handed. The experiment was approved by the Life Sciences Ethics Committee at the University of Sussex.

2. 1. 2. *Materials:* A light emitting diode attached to a tapper was affixed with transparent sticky tape to the first and last digits, and a black dot marked the centre point between the two sites (see Figure 2). Tactile cues were admitted with MST4S 12-V solenoid tappers that produced a blunt and brief tap of 1.5 millimetres diameter. Visual targets were presented with green light emitting diodes of 64.3 cd/m^2 luminance and a diameter of 3 millimetres. Participants were asked to sit up straight and close to the table so the distance between their eyes and the hand was approximately 50 centimetres. A microphone was placed in front of the participants in order to record reaction times of responses and the experimenter used a score sheet to note the accuracy of these responses. The stimuli were presented using E-Prime 2.0, although the screen remained black during the time of experimentation. For seven of the participants the apparatus was set up on their dominant hand and six were tested on their non-dominant hand. Headphones sounding white noise were placed over participants' ears so that they could not hear the sound of the taps.

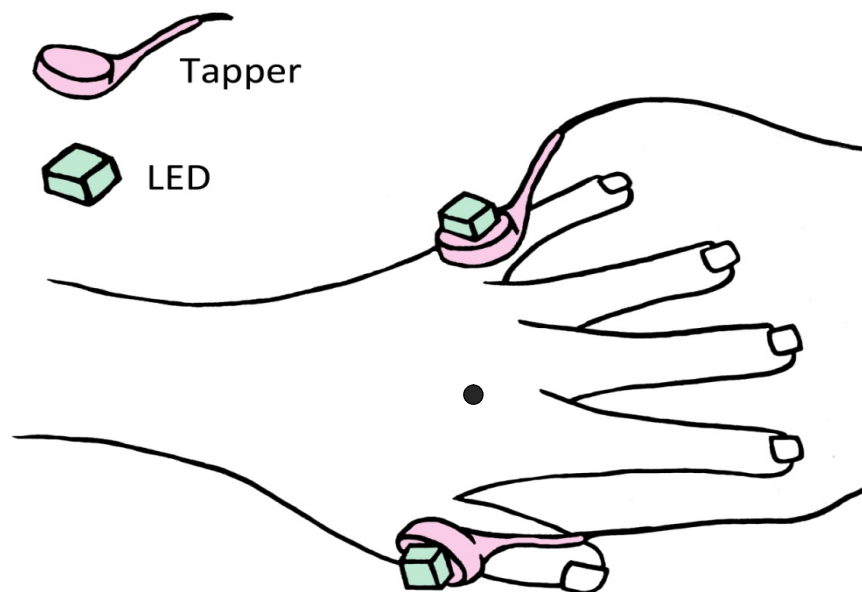


Figure 2: Set-up of apparatus. Solenoid tappers attached to the first and fifth digits with affixed green light emitting diodes. Dot in the centre of the hand acted as visual fixation point.

2. 1. 3. *Design and Procedure:* The effect of congruency on spatial discrimination reaction time was measured in a within-subjects design. There were an equal number of congruent and incongruent trials and stimuli appeared equally on either the left or right side. There was no predictive relationship between the cue and target, i.e. there was a 50% chance

of the target appearing on the same side as the cue whether this was on the right or left of the fixation point. Three experimental blocks of 160 randomised trials were preceded by a practice block of 16 trials (this block was not analysed).

Participants were seated at a table in a dimly lit cubicle to reduce extraneous environmental confounds whilst allowing the hand placed on the table to remain visible. Participants were instructed to keep focused on the fixation point at all times and were reminded of this between blocks. On every trial the participants would experience a tactile tap to either the first or fifth digit followed 100 milliseconds later by a flash of light on either the first or fifth digit. Participants were instructed to ignore the tap and vocally indicate as quickly and accurately as possible whether the visual target appeared on either the "right" or "left" of the fixation point. Prior to testing participants were familiarised with the visual and tactile stimuli and were given approximately five minutes to adapt to the dim lighting. At the end of the experiment participants were debriefed, given the opportunity to ask questions and received three course credits for their time.

2. 2. Results and Discussion

Mean accuracy rate in "right or left" discrimination task was 98.17%. Error trials, reaction times three standard deviations above the means and reaction times below 100 milliseconds were removed from the analysis. No significant difference in reaction time of congruent and non-congruent trials was found between participants tested on the dominant hand and those tested on the non-dominant hand ($F_{(1,11)} = 1.827$, $p = .204$). These were henceforth treated as a single group.

Reaction times were significantly faster when the cue and target congruently occurred on the same side of the fixation point ($t_{(12)} = -14.531$, $p < .001$). On congruent trials ($M = 418.43$, $SD = 27.82$) participants responded on average 46.17 milliseconds faster than on incongruent trials ($M = 464.60$, $SD = 50.12$), indicating that the tactile cue aided the visual spatial discrimination task. Further analyses were carried out in order to investigate whether these findings were valid for each participant at an individual level. All participants showed significantly faster reaction times for congruent over incongruent stimuli (all $p < .016$; see Figure 3).

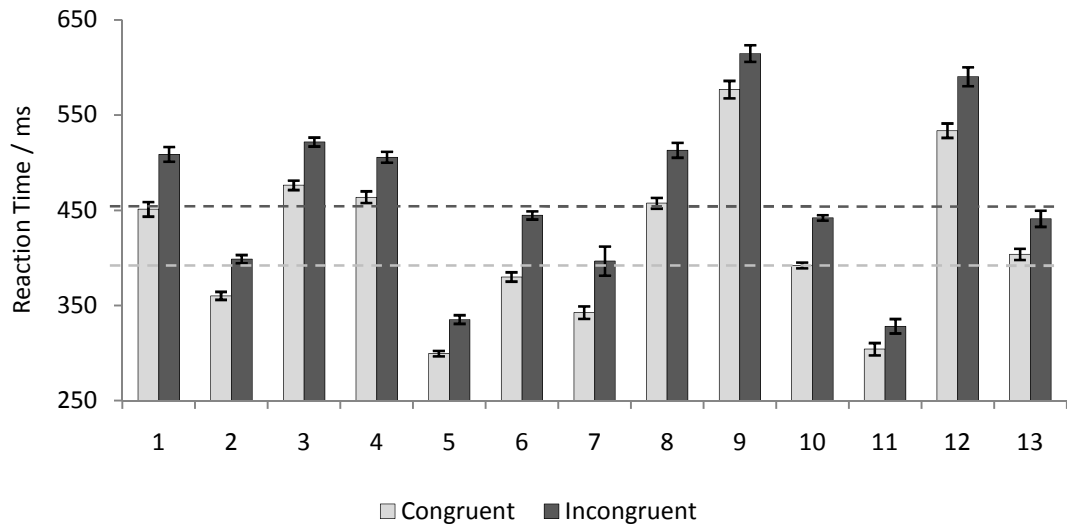


Figure 3: Means and standard errors of reaction times for congruent and incongruent trials for individual participants on visual spatial discrimination task. Light and dark dotted lines represent group congruent and incongruent means respectively.

In line with the hypotheses, and findings by Driver and Spence (1998a, 1998b, 2000; Driver, 2001), spatial discrimination decisions as to whether the location of the visual target was on the left or right were significantly faster if the tactile cue was congruently presented in the same location as the visual target rather than incongruently on the contralateral side to the target. Not only was this effect found overall, but there was a significant difference between congruent and incongruent trials on an individual basis for each participant. Moreover, there was no significant difference between congruent and incongruent trials dependent on whether the experiment was set up on the dominant or non-dominant hand, indicating that side of amputation should not act as a confounding variable in the test on upper-limb amputees.

3. Experiment 2

Experiment 1 successfully replicated results reported by Driver and Spence (1998a, 1998b, 2000; Driver, 2001) but in a one-handed paradigm; reaction times in spatial detection of a light stimulus were significantly faster if the tapper cue was congruently presented on the same side of the hand than when it was incongruently presented on the other side. Experiment 2 aims to investigate whether this was also true in upper-limb amputees using their non-amputated limb (control condition) and to see if reaction times were also faster

when the tactile cue was presented to the facial areas which referred sensations to the phantom limb (referred sensations condition). In a third condition the tactile cue was presented to the side of the face contralateral to the amputation, and it was hypothesised that as these areas do not influence phantom sensations, there should be no difference between the reaction times based on the side of the face on which the taps are experienced. To summarise, this experiment consisted of the following three conditions:

- (1) Tactile stimulation on real hand, visual stimulation on real hand (control condition, same as Experiment 1 but using amputees).
- (2) Tactile stimulation on ipsilateral face, visual stimulation on rubber hand placed in the same location as the phantom (this is the main condition of interest).
- (3) Tactile stimulation on contralateral face, visual stimulation on rubber hand placed in the same location as the phantom (this is a second control condition to ensure that face-hand cueing effects are specific to locations eliciting referred sensations).

3. 1. Method

3. 1. 1. Participants: Three individual cases with only one upper-limb amputation took part in this study. The participants were all male, right-handed prior to amputation and acquired their amputation as a consequence of a traumatic injury. Participants were recruited through the Sussex Rehabilitation Centre in Brighton, and had previously completed a questionnaire regarding limb deficiency and phantom limb sensations. The experiment was sponsored by the Life Sciences Ethics Committee at the University of Sussex and approved by the Brighton East Research Ethics Committee of the National Health Service (see Appendix A).

SBG, aged 50, had lost his left arm below the elbow in a motorcycle accident six years prior to testing date. He did not wear a prosthetic limb anymore because the shoulder muscles had weakened and struggled to carry the weight. SBG felt a constant burning and tingling ache in the phantom arm, and experienced shooting pains about once a day. The phantom limb felt to have full mobility and was of normal length and size. SBG did not recall ever having experienced or noticed referred sensations previous to our testing.

GJ, aged 64, had lost his right arm above the elbow in a tractor accident 46 years prior to testing date. He used a cosmetic prosthetic arm on an irregular basis, and despite having a telescoped phantom limb, it felt embodied within the prosthesis when it was on and shrunk

when it was removed. GJ's phantom pain resembled the pain he experienced in the accident previous to amputation; the limb was chopped by the tractor in seven places and he could still feel them all. He could both choose to move his phantom limb, and it would instinctively reach out if he needs to gain stability. GJ did not recall ever having experienced or noticed referred sensations previous to our testing.

SC, aged 45, had lost his right arm just above the elbow in a road traffic accident 24 years prior to testing date. He reported that the phantom limb could occupy the same space as the prosthetic limb and it could be moved in accordance with it. His original prosthesis felt too short, so he had it lengthened to fit the phantom limb. When he does not wear the prosthetic limb, SC's phantom arm is stuck at a perpendicular angle and the phantom fingers are clenched into a fist, but the limb as a whole felt like it could be moved through shoulder movement. About once a week, SC experienced a throbbing painful sensation in his phantom limb. SC did not recall ever having experienced or noticed referred sensations previous to our testing.

3. 1. 2. *Materials:* The set-up was identical to that of Experiment 1, but under the two test conditions the tappers were affixed to the participant's face and the light emitting diodes were attached to a rubber hand positioned in front of the participants at an angle at which the limb could be perceived as their own (see Figure 4). A paintbrush was used to locate two regions on the face that reliably (on two testing occasions separated by approximately six months) produced specific referred sensations in the phantom limb for one of the test conditions, and two regions that did not produce any such sensations for the other test condition. In both of these conditions the light emitting diodes were positioned in the locations to which sensations were referred to on tactile stimulation of the face. For example, in SBG, touch just under the left eye induced a tactile sensation on the back of the phantom left hand, so one of the tappers was placed under that eye (t1, test with referred sensations, Figure 4) and its corresponding light stimulus was placed on the back of the rubber hand (L1, both test conditions, Figure 4); similarly the second tapper was attached to the left of the lips (t2, test with referred sensations, Figure 4) because it induced a referred sensation in the location of the back of the phantom forearm where the second light stimulus was placed on the rubber limb (L2, both test conditions, Figure 4). In the test condition without referred sensations the light stimuli were positioned in the same locations as in the condition with

referred sensations, but the tappers were located in two locations on the contralateral side of the face that did not cause any referred sensations.

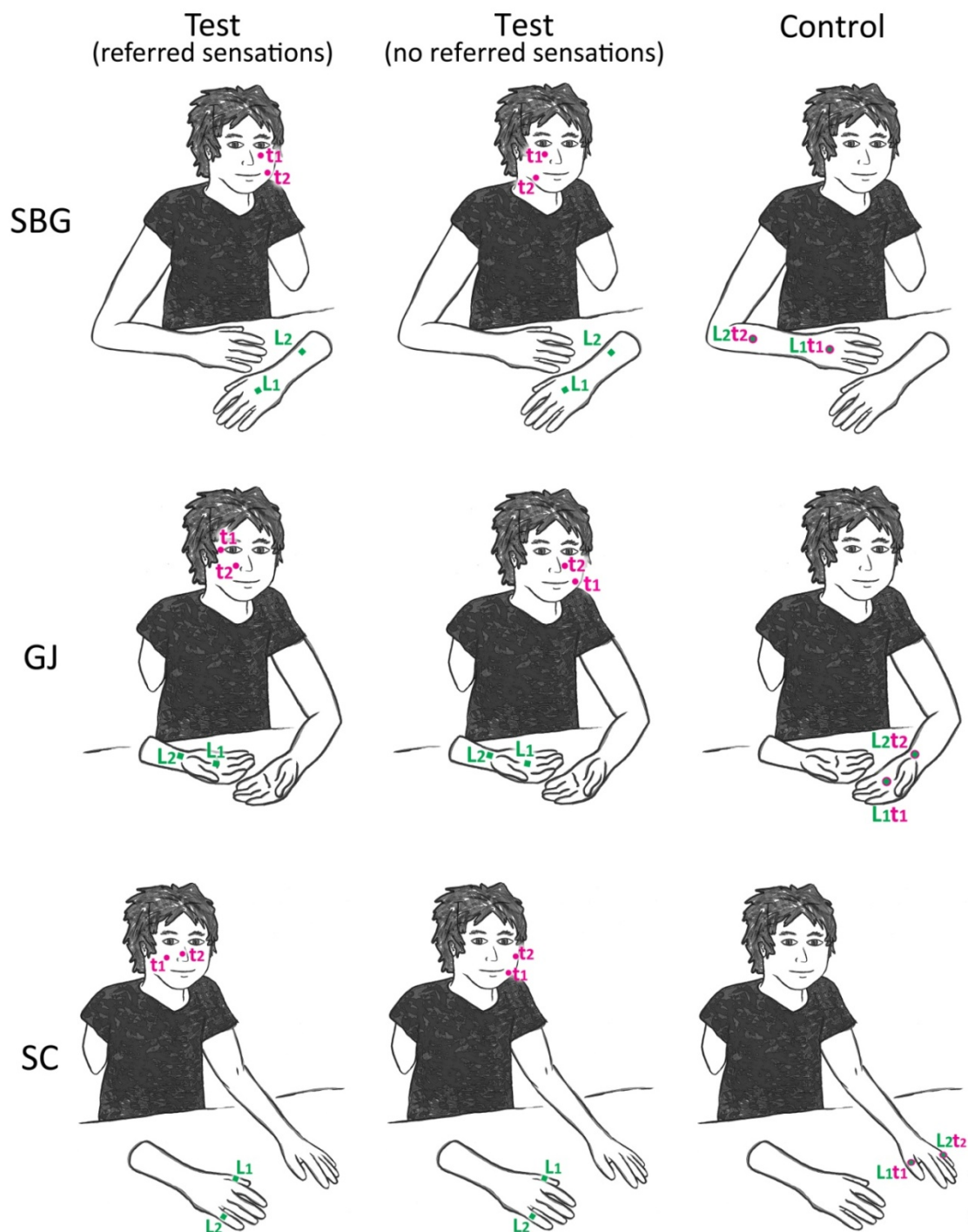


Figure 4: Experimental set-up for each of the three amputees and each condition. Green dots indicate the locations of the green light emitting diodes and pink dots indicate the locations of the solenoid tappers. A black fixation dot indicated the centre point between the two diodes.

In SBG these sites were nearly homologous to those in the test condition, but for GJ and SC one or both (respectively) of the homologous sites also produced referred sensations in the phantom limb, and therefore other sites were selected. A black sticker marked the centre point between the two lights on the rubber hand, and participants were instructed to use this as a visual fixation point. For the control condition, homologous sites to the visual locations in the other two conditions were used for both visual and tactile stimuli to verify that standard selective attention cuing tasks were unaffected by amputation, and to investigate whether the same pattern of results were found in amputees as in the normal-bodied population tested in Experiment 1.

3. 1. 3. Design and Procedure: In a similar fashion to Experiment 1, there were an equal number of congruent and incongruent trials, stimuli appeared equally on either the left or right side and there was no predictive relationship between the cue and target. Three experimental blocks of 100 randomised trials were presented in each of the three conditions yielding 900 trials in total. The conditions were carried out in a different random order for each of the three participants, and the experiment lasted a total of approximately one hour including set-up time. The procedure was otherwise identical to that of Experiment 1.

3. 2. Results and Discussion

Mean accuracy rate in "right or left" discrimination task across the three participants was 98.44% in the control condition, 98.67% in the test condition with referred sensations and 97.67% in the test condition without referred sensations. Error trials, reaction times three standard deviations above the means and reaction times below 100 milliseconds were removed from the analysis. Each participant was treated as an individual case study, and a 3 (set-ups) x 2 (congruency) repeated measures ANOVA was conducted for each participant. A significant main effect of set-up was found for all participants (SBG: $F_{(2,542)} = 45.876$, $p < .001$; GJ: $F_{(2,532)} = 6.186$, $p = .002$; SC: $F_{(2, 522)} = 14.59$, $p < .001$), but an overall significant effect of congruency was only revealed for SBG ($F_{(1,271)} = 31.607$, $p < .001$) who showed significantly lower reaction times in congruent trials ($M = 445.990$, $SE = 5.086$) than incongruent trials ($M = 463.098$, $SE = 5.219$). Significant interactions between set-up and congruency were found for all three participants (SBG: $F_{(2,542)} = 31.607$, $p < .001$; GJ: $F_{(2,532)} = 4.684$, $p = .010$; SC: $F_{(2, 522)} = 17.965$, $p < .001$), indicating that some set-ups may have produced a significant congruency

effect, whilst others did not. Independent samples t-tests were performed for each set-up condition in order to investigate for which a congruency effects occurred, and paired samples t-tests were used to investigate the differences in reaction times between the three set-ups.

Figure 5 contains the data of SBG. An independent samples t-test revealed that this participant showed the same pattern of results for the control condition as members of the general population tested in Experiment 1; when the tactile cue and visual stimulus were presented in the same spatial location, reaction times were significantly faster if the cue was congruently indicative of the stimulus location ($M = 394.88$, $SD = 94.26$) than on incongruent trials ($M = 480.45$, $SD = 114.70$; $t_{(289)} = -6.96$, $p < .001$; see Figure 5, Control). In contrast to the hypotheses there was no significant congruency effect in the test condition with referred sensations ($t_{(292)} = -.116$, $p = .908$), but there was a significant difference between congruent ($M = 520.84$, $SD = 114.02$) and incongruent trials ($M = 485.02$, $SD = 105.52$) for the test condition without referred sensations, albeit in the reverse direction ($t_{(286)} = 2.77$, $p = .006$), i.e. reaction times were significantly faster in the incongruent trials than the congruent ones. However, paired samples t-tests showed that SBG's reaction times were overall slower in the test condition without referred sensations ($M = 502.93$, $SD = 111.11$) than in the test condition with referred sensations ($M = 426.44$, $SD = 80.74$; $t_{(281)} = -8.957$, $p < .001$) and the control condition ($M = 436.93$, $SD = 113.06$; $t_{(278)} = 7.354$, $p < .001$). There was no significant difference in overall reaction times across congruency levels between the test condition with referred sensations and the control condition ($t_{(284)} = -1.048$, $p = .296$).

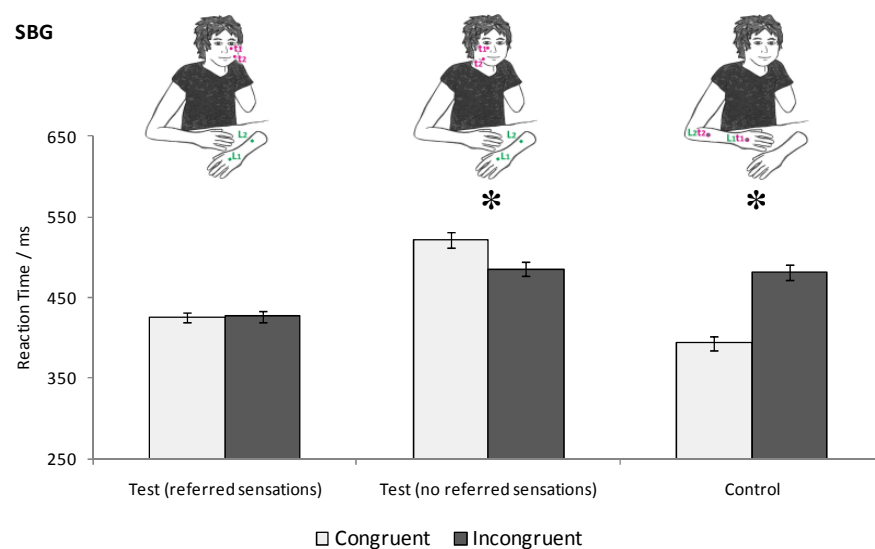


Figure 5: Means and standard errors of reaction times for congruent and incongruent trials for SBG on visual spatial discrimination task at three different types of experiment set-up.

A similar pattern of results was produced by GJ and SC (see Figure 6). Like SBG, and the normal-bodied population in Experiment 1, both GJ and SC performed significantly faster in "right or left" discrimination when both the tactile cues and visual stimuli were set up on the intact hand, and the cue was presented on the same side of the hand as the stimulus (GJ: $M = 368.03$, $SD = 67.98$; SC: $M = 507.68$, $SD = 79.48$) than when the cue was presented incongruently on the other side (GJ: $M = 387.32$, $SD = 65.27$, $t_{(286)} = -2.454$, $p = .015$; SC: $M = 567.05$, $SD = 70.35$, $t_{(295)} = -6.812$, $p < .001$; see Figure 6, Control). GJ and SC both showed a significant difference between the congruent and incongruent trials in the test condition with referred sensations (GJ: $t_{(289)} = 2.325$, $p = .021$; SC: $t_{(286)} = 2.938$, $p = .004$), and not for the test condition without referred sensations (GJ: $t_{(283)} = 1.205$, $p = .229$; SC: $t_{(285)} = -.485$, $p = .628$). However the differences that emerged were in the opposite direction to that predicted; reaction times were significantly faster for the incongruent trials (GJ: $M = 385.31$, $SD = 67.49$; SC: $M = 552.23$, $SD = 107.50$) than the congruent ones (GJ: $M = 404.10$, $SD = 70.31$; SC: $M = 598.94$, $SD = 157.61$).

In GJ reaction times in the test condition with referred sensations were significantly slower ($M = 394.80$, $SD = 69.45$) than in the test condition without referred sensation ($M = 371.86$, $SD = 86.50$; $t_{(275)} = 3.348$, $p = .001$) and the control condition ($M = 377.48$, $SD = 67.25$; $t_{(280)} = 3.090$, $p = .002$). There was no significant difference in overall reaction time between test condition without referred sensation and the control condition ($t_{(274)} = -.679$, $p = .498$). In SC reaction times were significantly faster in the control condition ($M = 537.07$, $SD = 80.66$) than in the test condition with referred sensation ($M = 575.42$, $SD = 136.69$; $t_{(284)} = 4.064$, $p < .001$) and the test condition without referred sensations ($M = 586.40$, $SD = 103.71$; $t_{(274)} = 5.857$, $p < .001$). There was no significant difference in overall reaction time between the two test conditions ($t_{(265)} = -1.169$, $p = .244$).

In summary, like the normal-bodied participants tested in Experiment 1 and studies outlined by Driver and Spence (1998a, 1998b, 2000; Driver, 2001), when the tactile cue is congruently presented in the exact same location as the visual target, reaction times of upper-limb amputees are faster than when the cue and target are incongruently presented on contralateral sides of the hand. Where a significant difference between congruent and incongruent trials was found in the test conditions, this was always in the opposite direction to the prediction whether referred sensations were targeted (as in SBG) or not (as in GJ and SC), i.e. the reaction times were faster on the incongruent trials. However, a closer inspection of the experimental set-ups reveals that albeit these trials were *incongruent* when considering the destination of their referred sensations, they would be considered as *congruent* trials in a

classical spatial attention orthogonal cuing task, as the cues are on physically opposite sides to the targets. For example, in test condition without referred sensations in SBG, the tapper nearer the nose (t1, test without referred sensations, Figure 5) was left of the tapper on the jaw line (t2, test with referred sensations, Figure 5) and thus cued the visual target on the left of the arm (L2, test with referred sensations, Figure 5). Similarly, tapper t2 on the right side of the facial set-up cued the flicker L1 on the right side of the arm. Hence, the trials termed in this paradigm as incongruent for referred sensations, have exhibited a classic congruency effect in crossmodal attention orthogonal cuing. As the same is true of the test condition with referred sensations in GJ and SC, the results indicated that perhaps referred sensation after amputation were not strong enough to interfere with such a robust perceptual effect.

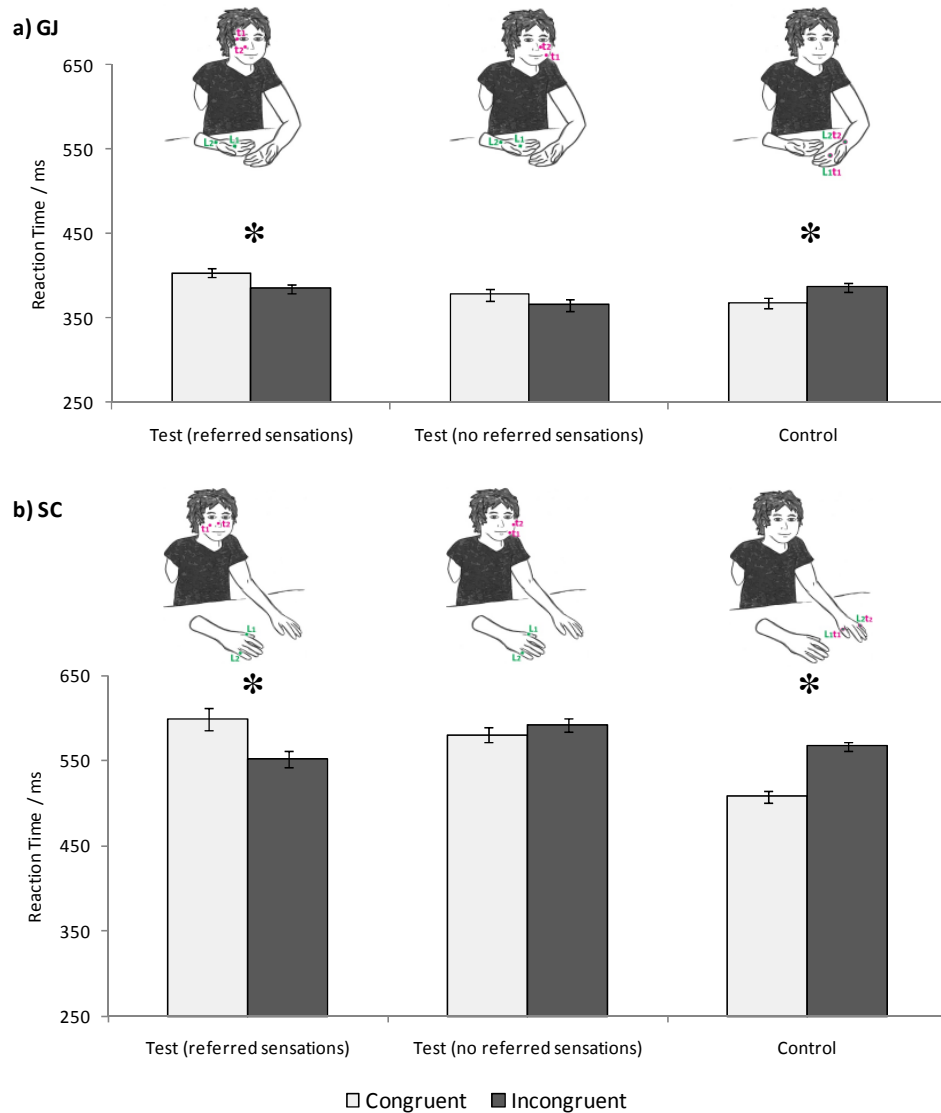


Figure 6: Means and standard errors of reaction times for congruent and incongruent trials for GJ (a) and SC (b) on visual spatial discrimination task at three different experiment set-ups.

This begs the question as to why no congruency (or incongruency) effects are found in the test condition with referred sensations in SBG and the test conditions without referred sensations in GJ and SC. As is illustrated in Figure 4, in these conditions the tactile tappers are nearly completely vertically aligned on the face and thus neither t1 nor t2 directly cued either of the light stimuli, and therefore the taps received by the face had no influence on the visual spatial discrimination task on the rubber hand. Where a significant effect of congruency *was* found in the test conditions, reaction times altogether tended to be significantly slower than in the control conditions, suggesting that the task was more difficult when the cues and targets were on separate parts of the body, i.e. face and hand, than when they were both presented in the same locations on the hand.

4. General Discussion

Most studies investigating the referral of sensations in amputees from the body to the phantom limb have relied on self-reports (Ramachandran *et al.*, 1992a; Ramachandran *et al.*, 1992b; Halligan *et al.*, 1993; Halligan *et al.*, 1994; Doetsch, 1997; Ramachandran and Hirstein, 1998; Kern *et al.*, 2006) or neuroimaging correlations (Elbert *et al.*, 1994; Knecht *et al.*, 1996; Pascual-Leone *et al.*, 1996; Borsook *et al.*, 1998; Davis *et al.*, 1998; Montoya *et al.*, 1998; Grusser *et al.*, 2001; Grusser *et al.*, 2004) to explore this phenomenon. The current study aimed to introduce an objective experimental paradigm that could be employed as a standardised empirical measure of referred sensations in amputees. Based on experiments of orthogonal cuing on multimodal spatial attention by Driver and Spence (1998a, 1998b, 2000), we hypothesised that a tactile cue to a referred sensations target zone on the face would decrease the reaction time in spatial discrimination of a visual target if it was located at the site where phantom touch sensations were referred to. Conversely, the results demonstrated that not only did referred sensation not have an impact on spatial discrimination decisions, but that the physical location of the tactile stimuli on the face did. When one of the tactile cues was clearly located to one side or the other on the participant's face, its stimulation cued the visual target on that side of the rubber hand, regardless of whether it was producing referred sensations directed otherwise or not. That is, the mapping between tactile stimulation on the face and visual stimulation on the rubber hand was determined by their alignment in *physical* space rather than their alignment with respect to phantom limb referred sensations.

Experiments investigating multimodal selective attention using this technique have proven that orthogonal cuing produces very strong and robust effects (for reviews see Driver, 2001; Eimer and Driver, 2001). This might explain why the real touch on the face had a greater influence on the spatial attention task than referred sensation in the phantom limb, which amputees often report as fainter than actual touch, such as the tingling sensation described by Patient VQ in Ramachandran and Hirstein (1998). Moreover, as there is currently no objective way of measuring this, it is also possible that participants did not actually experience a referral of the tap sensations from the face to the phantom limb at all. Ramachandran *et al.* (1992b) found that a light pinprick, a sensation similar to that produced by the solenoid tappers used here, was not sufficient to lead to referred sensations in all amputees. When participants were questioned about this they reported so much was going on from the taps to the lights and the face to the rubber hand that they weren't sure whether or not they were experiencing referred sensations. Regardless of whether they were actually experiencing touch in their phantom, it is evident that classical orthogonal cuing takes precedent over any referred phantom sensations the amputees might have experienced.

Although the current experiment has not successfully managed to introduce a new methodology for measuring referred phantom sensations in amputees, we hope that it has highlighted the importance of doing so. There are many unanswered questions in this field, and without a means to measure referred sensations these problems may remain unsolved. For instance, many researchers have reported the problem of finding a topographical pattern in the trigger zones that cause referred sensations as originally described by Ramachandran *et al.* (1992a; 1992b). Based on a single case study, Halligan *et al.* (1994) suggest that the topographical mapping of the phantom hand on the face reorganises as time progresses, and Knecht *et al.* (1996) even concluded that there was no relationship between cortical reorganisation and a particular pattern of referred sensations. As such they disregarded the locations of stimulation sites and focused on the number of points from which sensation was referred. However, not every inch of the skin's surface is normally tested and this risks that potential trigger zones could easily be missed.

Another question that has risen is whether or not referred sensations are modality specific. In Ramachandran *et al.*'s (1992a; 1992b) original reports there appeared to be a coupling between temperature, movement and duration of the stimulus presented and referred sensations, i.e. touch with warm water would lead to a warm dripping sensation in the phantom limb. However, later studies have often reported that regardless of what was used as a stimulus the sensations in the phantom were always of similar quality (e.g. Knecht *et*

al., 1996), or that only stimuli that applied pressure on the skin, e.g. cotton bud or finger, produced referred sensations in the phantom (e.g. Halligan *et al.*, 1993; Sathian, 2000). Ramachandran *et al.* (1992b) themselves found referred sensations in various modalities for only one of their two participants, and explained that "[t]he reason for this difference between the two patients is not clear" (p. 585). It is hoped that by developing an objective standardised measure for identifying referred phantom sensations, the changes that occur to them and the differences between individual amputees could be quantitatively measured and scientists would possess better tools for unveiling the answers to some of these queries and theories.

The future could look at further exploring referred sensations phenomena by using the rubber hand illusion. It would be of particular interest to see if proprioceptive drift towards the rubber hand is found when trigger zones of the face are stimulated as the results by Ehrsson *et al.* (2008) might suggest. If the referred sensations from the face are qualitatively similar to those experienced from the stump, it can be assumed that stroking the face congruently to the stroking of a rubber hand would cause the phantom hand to be perceived as closer in space to the rubber hand. If so, an investigation into differences in amount of drift or duration of drift could provide insight into individual differences between amputees based on time since amputation and perceptual qualities, such as phantom solidity, mobility and telescoping. It is premature to propose what could be discovered with a measure of referred sensations as the development of such a paradigm is in its youth, but it is clear that there is much more to be discovered in our understanding of phantom limb phenomena, and referred sensations in particular.

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Appendicies



National Research Ethics Service

Brighton East Research Ethics Committee

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25 June 2008

Dr Jamie Ward
Senior Lecturer
University of Sussex
Department of Psychology
University of Sussex
Falmer, Brighton
BN1 9QH

Dear Dr Ward

Full title of study: Cognitive and neural correlates of phantom sensations in amputees
REC reference number: 08/H1107/73

Thank you for your letter of 02 May 2008, responding to the Committee's request for further information on the above research [and submitting revised documentation], subject to the conditions specified below.

The further information has been considered on behalf of the Committee by the [Chair] [Vice-Chair].

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation [as revised].

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA). There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Application	1	31 March 2008
Investigator CV		
Protocol	1	31 March 2008
Covering Letter		07 April 2008
Compensation Arrangements		
Participant Information Sheet: (EEG)	3	29 May 2008
Participant Information Sheet: (fMRI)	4	25 June 2008
Participant Information Sheet: (questionnaire)	2	29 May 2008
Participant Information Sheet: (computer task)	3	29 May 2008
Participant Consent Form	2	25 March 2008
Response to Request for Further Information		02 May 2008
Questionnaire (non validated)	2	29 May 2008
Review by Prof Walsh		04 February 2008
Flow diagram		
Letter to Dr	1	25 March 2008
Invitation letter to participant	1	25 March 2008

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website provides guidance on these topics, which is updated in the light of changes in reports or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/H1107/73**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely



Dr Paul Seddon
Chair

Email: nischinth.cherodian@bhcpct.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: Professor Jennifer Rusted
Chair of Life Sciences Ethics Committee
University of Sussex
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BN1 9QH

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D Phil Student
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R&D office for Brighton and Sussex University Hospitals NHS Trust

Limb Deficiency and Phantom Limb Questionnaire

Name : _____	
Sex : male / female	Date of Birth : _____ Age at amputation : _____
Address : _____	
Email : _____	Phone : _____

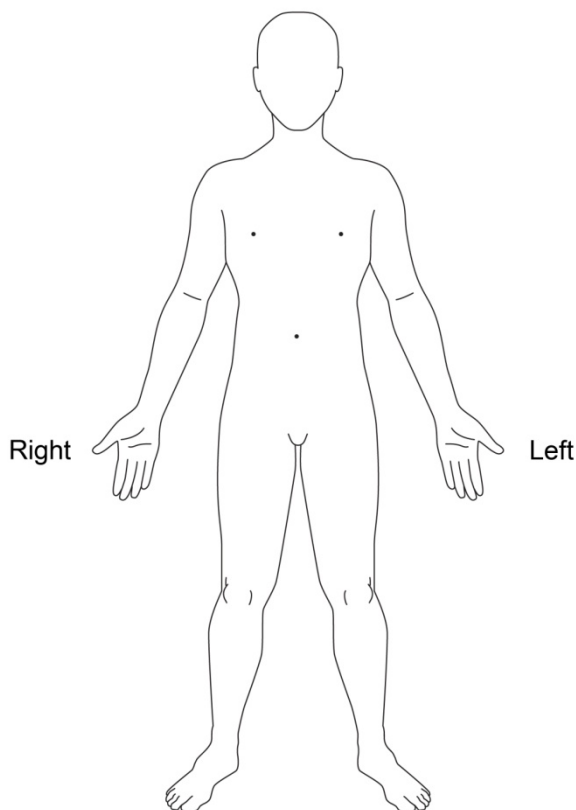
Please feel free to add notes and give extra details to better describe your experiences. Should you need any assistance completing this questionnaire do not hesitate to contact Ms Aviva Goller via telephone or email (details can be found below). Please note: N/A refers to "not applicable" throughout.

Handedness: Prior to amputation I would write with the ☐ Left ☐ Right ☐ Both ☐ N/A

Footedness: Prior to amputation I would kick a ball with the ☐ Left ☐ Right ☐ Both ☐ N/A

Please indicate the location of your amputation or other limb deficiency.

(Draw it and indicate its distance in centimeters or inches from either the elbow or knee.)



Please describe reasons for your limb deficiency (e.g. congenital due to...; amputation resulting from...)

Prosthesis

Have you ever worn one? ☐ Yes ☐ No

If yes, it was

☐ Electric ☐ Non-Electric ☐ Other

When did you start using it? _____

Do you still wear it? ☐ Yes ☐ No

If no, when did you stop? _____

Why? _____

contact us

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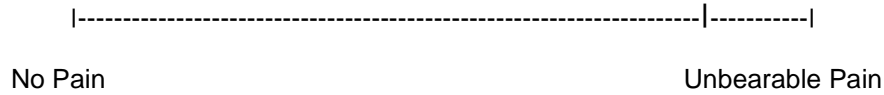
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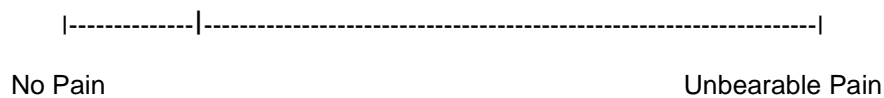
Instructions on How to Use a Visual Analogue Scale

The following line represents a scale of various levels of pain with “No Pain” at one extreme and “Unbearable Pain” at the other extreme. Please indicate where your experiences rank on such a scale by putting a straight line through this line.

Example 1: This individual experiences severely intense pain, but this feeling is not yet unbearable.

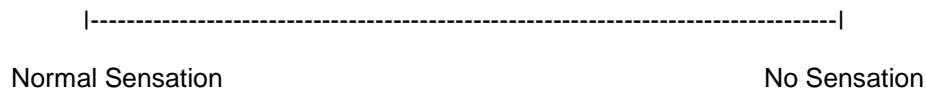


Example 2: This is a person undergoing moderate, yet noticeable, pain.

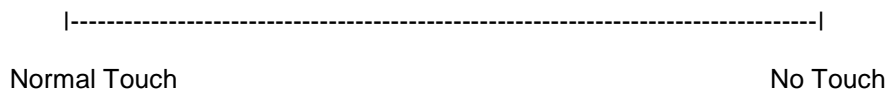


BEFORE Amputation – your last conscious experience of the limb

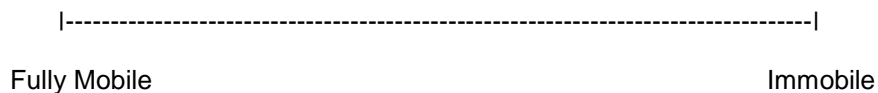
To what extent could you **feel the presence** of the limb *immediately before* amputation?



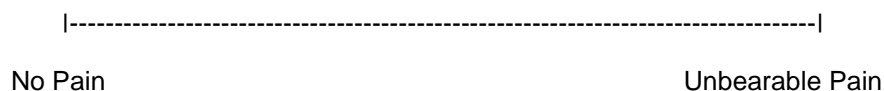
To what extent could you feel **touch** to the limb *immediately before* amputation?



To what extent could you **move** the limb *immediately before* amputation?



How strong was the **pain** in the limb *immediately before* amputation?



What was the cause of this pain (e.g. infection, cancer, accident)? _____

How long did this pain persist *prior* to amputation?

- ☐ Several days ☐ One week ☐ One month ☐ Several months ☐ More than six months

Where in the limb was this pain located?

- ☐ In the portion that was saved, i.e. that remained after amputation
- ☐ In the part that was amputated
- ☐ In the entire limb, i.e. both amputated and remaining
- ☐ Other: _____

AFTER Amputation

How strong was the **pain** in the limb *immediately after* amputation (i.e. as soon as the pain killers wore off)?

|-----|

No Pain

Unbearable Pain

Please describe this pain: _____

How long did this pain persist *after* amputation?

- ☐ Several days ☐ One week ☐ One month ☐ Several months ☐ More than six months

Where in the limb was this pain located?

- ☐ In the portion that was saved, i.e. the remaining stump
- ☐ In the part that was amputated, i.e. the phantom limb
- ☐ In the entire limb, i.e. the stump and phantom
- ☐ Other: _____

Were there any complications after amputation (such as stump wound infections, presence of neuromas, presence of contractures)? Did you have multiple operations? _____

Phantom Limb Experiences

Often after amputation (or even for congenitally absent limbs) people report that they can still feel the presence of their missing limb. These experiences are known as phantom limbs and are sometimes manifested as voluntary movements, tingling feelings or even pain.

Have you had any phantom limb experiences in/of the missing limb?

- ☐ Yes ☐ No

Please describe your phantom sensations: _____

Does / did the phantom limb feel similar in quality to the intact limb? ☐ Yes ☐ No

How long after your amputation did the experiences first appear?

☐ Immediately ☐ Within days ☐ Within one week ☐ Within one month
☐ After a few months ☐ More than six months later: _____ ☐ N/A

Do you still have any phantom limb experiences in/of the missing limb? ☐ Yes ☐ No

If no, when did they disappear? _____

How often do / did these **sensations** occur?

☐ Permanent ☐ Several times a day ☐ Once a day ☐ Several times a week ☐ Once a week
☐ Once a fortnight ☐ Once a month ☐ Less than once a month ☐ N/A

Please indicate the level of pain associated with the *phantom limb* (i.e. not the stump) at its worst.

|-----|
 No Pain Unbearable Pain

Is this pain feel similar in quality to the pain experienced prior to amputation? ☐ Yes ☐ No

How often does / did this pain occur?

☐ Permanent ☐ Several times a day ☐ Once a day ☐ Several times a week ☐ Once a week
☐ Once a fortnight ☐ Once a month ☐ Less than once a month ☐ N/A

Please describe this pain: _____

Is this pain associated with any events in daily life (e.g. stress, rest, exercise)? _____

Has the pain intensity changed since the amputation? ☐ Weaker ☐ Stronger ☐ No Change

Has the pain been treated (e.g. medication, physiotherapy, massage, amputation)? ☐ Yes ☐ No ☐ N/A

If so, how? _____

_____ Did the treatment help? ☐ Yes ☐ No ☐ N/A

Does seeing someone else *move* their equivalent limb ever cause your phantom limb to imitate their action?

☐ Yes ☐ No

Does seeing someone else *touched* ever trigger a corresponding feeling of touch to your phantom limb?

☐ Yes ☐ No

Does seeing someone else in *pain* ever cause sensation in your phantom limb?

☐ Yes ☐ No

Does the phantom limb ever mimic the sensations and actions of the intact limb?

☐ Yes ☐ No

Does it feel like you could carry out *combined movements* of the intact and phantom limbs (e.g. gesticulating or clapping)?

☐ Yes ☐ No

Can your phantom limb and intact limb co-exist in the same physical space?

☐ Yes ☐ No

Can you actively *choose to move* your phantom limb (e.g. to wiggle your fingers / toes)?

☐ Yes ☐ No

Does your phantom limb ever *move spontaneously* (e.g. to avoid being hurt or to instinctively grab hold)?

☐ Yes ☐ No

When you dream, is your missing limb present?

☐ Yes ☐ No

Does massaging the stump cause sensations in the phantom limb?

☐ Yes ☐ No

If yes, please describe: _____

Does your phantom *hand/foot* appear to be normal in size?

☐ Normal ☐ Enlarged ☐ Shrunken

Does your phantom *arm/leg* appear to be normal in length?

☐ Normal ☐ Longer ☐ Shorter

If longer or shorter, then by how much? _____

Can you actively stretch or contract your limb beyond normal length?

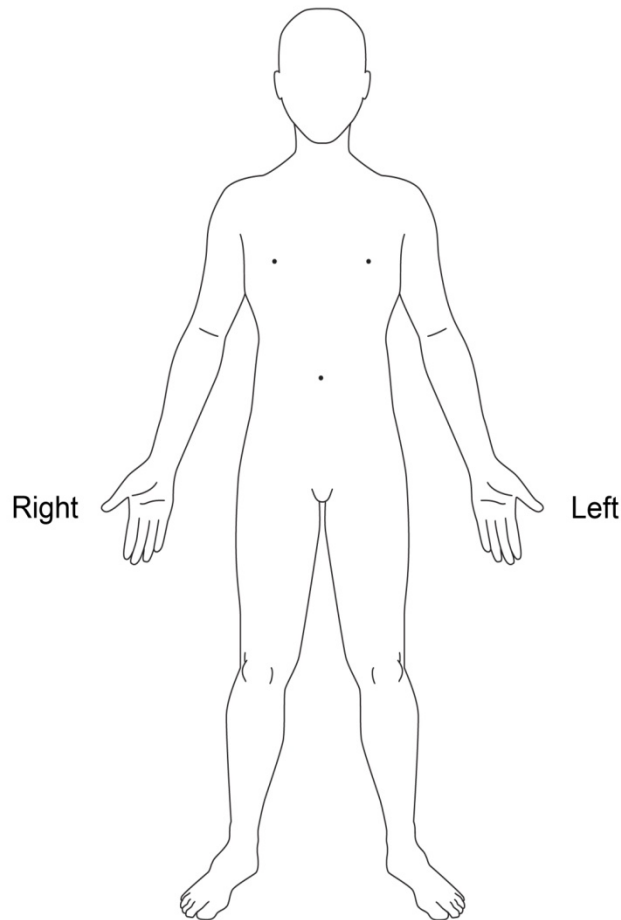
☐ Yes ☐ No

When wearing a prosthesis does / did your phantom limb occupy the same space as the prosthesis?

☐ Yes ☐ No ☐ N/A

Please indicate the location, size and length of your *phantom sensations*.

(Draw it and indicate its estimated distance in centimeters or inches from either the elbow or knee.)



Please provide a description of your phantom limb or any other relevant information (continue on a separate sheet if necessary). Does it itch? Does it burn? Does it tingle? Does it feel pressure? Does it feel like it doesn't belong to you? Is it stuck in one position? Can it adopt unnatural postures? Can it stretch or extract?

Thank You for Your Time.

Please return to Ms Aviva Goller by post or email (details at the bottom of first page)

To learn more about us please visit our website www.syn.sussex.ac.uk/phantomlimb



Phantom Pain Questionnaire

Surname : _____		First Name : _____	
Sex : male / female	Date of Birth : _____	Year of amputation : _____	
Email : _____		Phone : _____	
<i>I understand the information given in this questionnaire is confidential and my details will not be passed on without my consent. I am under no obligation to take part in further research unless I give further consent to do so. I have been given sufficient information about the research.</i>			
Signed : _____		Date : _____	

Please do add notes and give extra details to better describe your experiences. Should you need any assistance completing this questionnaire do not hesitate to contact Ms Aviva Goller via telephone or email (details can be found below).

Please note: N/A refers to "not applicable" throughout.

What was the cause of your amputation?

- ☐ Trauma (e.g. road accident or war injury) ☐ Cancer ☐ Vascular disease (e.g. diabetes)
- ☐ Other disease : _____ ☐ Other cause : _____

If your amputation was caused by trauma...

Did you lose your limb in the accident or at a later time in hospital?

- ☐ In the accident ☐ After the accident

How long after the accident did you lose your limb?

- ☐ Hours ☐ Days ☐ Weeks ☐ Months ☐ Years ☐ N/A

Were you conscious between the accident and the amputation? ☐ Yes ☐ No ☐ N/A

Were you on pain medication during this time? ☐ Yes ☐ No ☐ N/A

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BEFORE Amputation – your last conscious experience of the limb**Prior to amputation how long had you felt pain in your limb?**

_____ years _____ months _____ days

(please indicate a number)

Prior to amputation how *frequent* was the pain in your limb?

|-----|

never any pain

constant pain

Prior to amputation what was the *intensity* of the pain felt in the limb at its worst?

|-----|

no pain

unbearable pain

Prior to amputation* how intensely did you experience the following sensations in your limb?*Throbbing**

|-----|

none

severe

Cramping

|-----|

none

severe

Shooting Pains

|-----|

none

severe

Tingling

|-----|

none

severe

Itchiness

|-----|

none

severe

Numbness

|-----|

none

severe

Other : _____

|-----|

none

severe

- ☐ My phantom is a *constant* feeling that my missing limb is still present and a part of my body.
- ☐ I sometimes / always feel moving sensations in my phantom, such as chills or tingling.
- ☐ I sometimes / always experience discomfort or pain in my phantom, such as burning or cramping.
- ☐ Other :

_____ hours _____ days _____ months _____ years
(please indicate a number)

never any pain constant pain

A horizontal dashed line with vertical tick marks at each end. Below the left tick mark is the text "no pain". Below the right tick mark is the text "unbearable pain".

_____ minutes _____ hours _____ days ☐ constant
(please indicate a number)

☐ Rest (e.g. watching television) ☐ Bedtime or sleep ☐ Strenuous activity (e.g. exercise)
☐ Stress ☐ Verbal reference to amputation / phantom ☐ Seeing someone in pain
☐ Other :

☐ Massage to stump ☐ Pain medication ☐ Mirror therapy ☐ Acupuncture
☐ Rubbing the space where pain is felt ☐ Recreational drugs ☐ Mental imagery
☐ Other :

If your intact limb hurts do you also feel it in your phantom limb? ☐ Yes ☐ No ☐ N/A

Does seeing someone else in pain cause you to feel a similar pain in your phantom? ☐ Yes ☐ No

After amputation how intensely have you experienced the following sensations in your phantom?

Throbbing

|-----|
none severe

Cramping

|-----|
none severe

Shooting Pains

|-----|
none severe

Tingling

|-----|
none severe

Itchiness

|-----|
none severe

Numbness

|-----|
none severe

Other : _____

|-----|
none severe

With closed eyes, does the phantom limb feel the same or different to the intact limb and the rest of your body? ☐ Same ☐ Different

Is your phantom limb stuck in one fixed position? ☐ Yes ☐ No

Is there anything else you wish to share about your phantom pain and other phantom experiences?

The following questionnaire aims to investigate some personality traits. We are interested to find out if any of these may be linked to your phantom limb experiences and pain.

On a scale of 1-4 please indicate the degree to which you agree or disagree with each statement.

		Strongly Disagree	Disagree	Agree	Strongly Agree
1.	I really enjoy caring for other people.	1	2	3	4
2.	I can easily work out what another person might want to talk about.	1	2	3	4
3.	Friendships and relationships are just too difficult, so I tend not to bother with them.	1	2	3	4
4.	Seeing people cry does not really upset me.	1	2	3	4
5.	I can sense if I am intruding, even if the other person does not tell me.	1	2	3	4
6.	I often find it difficult to judge if something is rude or polite.	1	2	3	4
7.	I am good at predicting how someone will feel.	1	2	3	4
8.	I do not tend to find social situations confusing.	1	2	3	4
9.	If I say something that someone else is offended by, I think that is their problem, not mine.	1	2	3	4
10.	I can tune in to how someone else feels rapidly and intuitively.	1	2	3	4
11.	I find it difficult to explain to others things that I understand easily when they do not understand it first time.	1	2	3	4
12.	I usually stay emotionally detached when watching a film.	1	2	3	4
13.	I find it hard to know what to do in a social situation.	1	2	3	4
14.	I am quick to spot when someone in a group is feeling awkward or uncomfortable	1	2	3	4
15.	I tend to get emotionally involved with a friend's problems.	1	2	3	4

THANK YOU FOR YOUR TIME.

Please return to Ms Aviva Goller by post or email (details at the bottom of first page).

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