Phantom pain:

On the mechanisms involved and its potential treatment.

Rapportens samlede antal tegn
(med mellemrum & fodnoter): 155.592
Svarende til antal normalsider: 64,8

10. Semester, Psykologi
Speciale

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Aalborg Universitet
31. Maj 2016

Abstract

Phantom pain poses a great issue due to its high prevalence and the fact that it is difficult to manage clinically. Despite being thoroughly investigated, it continues to be a mysterious phenomenon. What is needed is to take a look at the general tendencies of phantom pain from a larger perspective and based on empirical evidence, speculate in some of the mechanisms involved, and from there on synthesize a potential treatment based on the accumulated knowledge. The aim of this study was to answer the question: How can the mechanisms involved in phantom pain be explained? First, empirical evidence for peripheral and central mechanisms were listed, as these were argued to play a role in the constitution of phantom pain. Among peripheral aspects are: Phantom pain is known to correlate with stump pain; Phantom pain can be modulated or exacerbated by ectopic discharge from a neuroma; Skin temperature at the stump is known to correlate with phantom pain. Among central aspects are: Sensitization of neurons located in the dorsal horns can affect phantom pain; Cortical reorganization correlates strongly with phantom pain; Phantom pain often seems to share characteristics with preamputation pain; Regional anesthesia is only able to reduce pain in some instances; Top-down processes like attention, depression or catastrophizing can exacerbate phantom pain. It is argued that since no stimuli from the periphery is necessary for phantom pain to occur, the central mechanisms must be of special importance.

The theory of predictive coding ascribes a key role to the top-down component. It considers phantom sensation as an expression of a "filling-in" mechanism, but cannot explain why the sensation is painful or the mechanisms of how the phantom emerges. The neuromatrix theory describes how components from the peripheral and central nervous system together constitutes phantom pain. It considers signals from the periphery to have a modulating role in painful experiences and not to be the cause, but it does not account for the proportions in which different components contribute to the sensation of pain, or why phantom pain emerges.

From the understanding that several mechanisms together constitute phantom pain and with a particular emphasis on the effects of top-down processes, a new hypothesis was formed. It was hypothesized that sensory and motor training of the phantom limb during hypnosis could reduce phantom pain. A study was designed to test this

hypothesis. In the control group the therapy consisted of hypnosis with relaxation being the main theme suggested. The therapy was set to be administered four times over the period of four weeks. Participants will be allocated to the groups with hypnotizability (SHSS:C) and pain intensity as primary and secondary stratification parameters respectively. Measures of pain intensity, unpleasantness, and frequency will be made before and after the intervention period as well as in a follow-up one month later. Additionally, Beck Depression Inventory (BDI-II) and Pain Catastrophizing Scale (PCS) are administered to uncover affective aspects of phantom pain. Measures of pain intensity and unpleasantness will also be made before and after each intervention to determine immediate effects of the therapy as well as the three consecutive days following therapy to obtain a measure more independent of the immediate effects.

To test the feasibility of the paradigm pilot data were obtained. Two participants were included "John" and "Peter" and only the intervention group was tested. John showed a substantial reduction in pain frequency in the measures of number of attacks on days with attacks (from 10 to 1), and in the duration of each attack (from 120 seconds to 60). A decrease was also observed in PCS (from 25-18) with the largest decrease in the subscale of helplessness. A small immediate effect was observed in pain intensity and unpleasantness in the first two sessions but not during the final two. A small immediate effect was observed in all session with Peter. However, no effects were seen in any other measures. It was suggested that the fact the participants were on pain medicine, might have caused a floor effect, due to the fact that they already at the start of the therapy rated pain low, why this should be abstained. To increase the effects on the general measure, it was argued that the hypnosis sessions could be supplemented with daily training tasks at home.

Conclusions regarding the effect of the therapy cannot be made, as this was a pilot study, however indications provided by the pilot data illustrate the paradigm as being feasible and can potentially be enhanced by the suggested elements. The full scale study is necessary to provide conclusions regarding the effect of the therapy.

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APPENDIX:

1. Introduction

After an amputation of an extremity virtually all will experience phantom phenomena. For most amputees these include sensations of presence of the missing limb. Some amputees even have vivid experiences of shape, length, posture and movement (Nikolajsen, 2012, p. 1). These sensations (*phantom sensations*) rarely pose a clinical issue, however 60-80% of amputees also have pain in the missing limb (ibid.). Pains in the missing limb (*phantom pains*) are often described as burning, cramping, crushing or lancinating (Ramachandran & Altschuler, 2009, p. 1694). Phantom pain can vary in intensity and frequency between amputees and over time. In fact, only a few is in constant pain (Nikolajsen, 2012, p. 3). Phantom pain is usually intermittent with episodes of pain attacks. Among amputees, the duration of these attacks can vary from seconds to several hours (ibid.), some having only a few attacks per month others several per day. Pain in the residual limb (*stump pain*) is unsurprisingly common immediately after amputation. Stump pain usually diminishes as healing progress, however for 5-10% severe pain persists (ibid.). Stump pain is often characterized by sufferers with the sensations of pressing, throbbing, burning, squeezing and stabbing (ibid.). Phantom and stump pain are not the only challenges amputees must face. These challenges includes impairment of physical functioning, adaptation to prosthesis use, financial changes (potential change in employment status), alteration of body image and self-concept, potential loss of independence, and other psychosocial adjustments (Moura et al., 2012, p. 702; Schaffalitzky et al., 2010, pp. 65-66). These stressors can lead to depression and in some cases to contemplation of suicide (Ramachandran & Altschuler, 2009, p. 1694).

In addition to having a large impact on the life of the amputee, phantom pain has unfortunately also proven very difficult to manage clinically. Suggestions in medicinal, surgical and other conventional therapeutic approaches have been made to reduce phantom pain. To mention a few: sympathectomy, stump manipulation, stump ultrasound, injection with local anesthetics and analgesics, transcutaneous nerve stimulation with discrimination training, nerve blocks, cordotomy, pharmacologic therapies, and myoelectric prosthesis. Unfortunately, these therapies have only been found to range from ineffective to slightly effective (Moura et al., 2012, p. 702). In other words, the effects of the treatments suggested are not satisfactory for neither

clinical management of phantom pain nor science trying to work out the mechanisms involved. For instance, strong analgesics such as morphine can have an effect on phantom pain for some amputees, but taking analgesics only treats the symptom, not the cause. Additionally, analgesics do not necessarily prevent the attacks from coming, but can make the pain more bearable. Even in case of extreme anesthesia such as a brachial plexus blockade where sensation and ability to move the arm is blocked, only three out of six participants experienced alleviation of phantom pain (Birbaumer et al., 1997). Due to the fact that brachial plexus blockade is performed by an injection and it renders the individual's residual arm temporarily paralyzed, it cannot be applied as a treatment in general. This study will be returned to later in **section 3.3.1.2.**

The most promising results in the treatment of phantom pain seem to emerge through studies taking a more unconventional approach. One of these unconventional approaches was taken by Ramachandran and Rogers-Ramachandran (1996) who investigated the intersensory effects on phantom limbs by providing visual feedback with a mirror. The patients were to place the residual limb in a box, on which a mirror was placed vertically and perpendicular to the patient's chest, facing towards the intact arm. The aim was to align the mirror, so that the reflection of the intact arm was superimposed on the phantom (Ramachandran & Rogers-Ramachandran, 1996, p. 379). The patient was then instructed to move both hands in synchrony, while observing the reflection in the mirror. Of the ten patients involved, six felt movement of the phantom corresponding to movement of the reflection (ibid., p. 377). Four of the five participants experiencing painful 'clenching spasms' in the phantom hand were capable of relieving this pain by opening both hands while using the mirror box (ibid. p. 379). Unfortunately, burning and lancinating pains remained completely unaffected by the procedure (ibid.).

Since then several studies have been attempting to replicate these finding, however the vast majority remain pilot, case or uncontrolled studies (e.g. MacLachlan et al., 2004; Darnall, 2009). The fact that the mirror box only partially alleviates pain is merely one of its limitations. Another limitation is that the mirror box requires the amputee has an intact limb, which reflection is to be superimposed on the phantom. This implicates that participants with bilateral amputations or paralyzed patients are excluded from the treatment.

Yet another unconventional approach was taken by MacIver and colleagues in 2008, who found that mental imagery could activate the sensory and motor cortices and would over a series of six sessions and daily exercises reduce cortical reorganization as well as intensity and unpleasantness of phantom pain. This study will be explained much more in detail in **section 4**, but for now it should be noted that MacIver et al. (2008) did not compare these results to a control group, thus not capable of concluding that the reduction of phantom pain was in fact due to the therapy administered, or other factors such as placebo, relaxation, etc. However, if the reduction of phantom pain reported is in fact due to mental imagery, it would illustrate that top-down processes play an important role in phantom pain. A top-down process is here to be understood as the regulatory effects higher brain functions (mental imagery) can have on lower (pain in the missing limb). Several studies have found that top-down processes can have a strong impact on phantom pain. This will be the topic of **section 4**.

The fact that treatments have been largely unsuccessful has only contributed to phantom pain being a rather mysterious phenomenon. Despite many studies have been investigating the effects of different treatments (Nikolajsen, 2012; MacIver et al., 2008; Ramachandran & Rogers-Ramachandran, 1996; Moura et al., 2012) very little is still understood about the phenomenon. Some of these studies may however prove very valuable in gaining an insight into the phenomenon from which the mechanisms involved in phantom pain might be hypothesized. This is a necessity if the conundrum of phantom pain is to be solved.

From a scientific point of view the interest in the phenomenon might be in the understanding of the mechanisms involved. From a clinical point of view the interest is in its treatment. The current project argues that the two fields should collaborate. The clinical research can uncover aspects and nuances of phantom pain which might foster speculations on the mechanisms involved. These speculations can be operationalized and help basic science to revise the general understanding of phantom pain. This revised understanding can then again help to guide future treatment.

1.1 Problem Statement

The sparse evidence for effective ways to treat phantom pain with the most promising therapies being largely uncontrolled, illustrates not only its complexity but also the need to observe it in a larger perspective. What is needed is to take a look at the general tendencies of phantom pain from a larger perspective, and based on the empirical evidence, speculate in some of the mechanisms involved and from there on synthesize a potential treatment based on the accumulated knowledge.

In this light, the aim of the current project is to explore the following question:

How can the mechanisms involved in phantom pain be explained?

The current study will seeks to account for the mechanisms which seem to be involved in phantom pain based on the promising indications some treatment methods have shown. In order to understand the mechanisms, **section 2** will lay the groundwork by introducing some of the necessary components of perception. The current project is not about perception in general, but will use the knowledge as a tool to help understand the basis of phantom pain. This section includes an account of the sensations of touch and pain, both relevant for phantom phenomena. In **section 3**, phantom limbs and the mechanisms thought to be involved will be accounted for and discussed. In **section 4** top-down processes and how they can influence phantom pain will be accounted for. Afterwards in **section 5**, the theoretical perspectives of predictive coding and the neuromatrix theory will be accounted for and discussed how they each illuminate phantom phenomena, and which implications remains. Neuroplasticity will be accounted for and discussed how it is an important factor in phantom pain. Hypotheses based on the empirical evidence and their implications on our understanding of phantom pain are then discussed.

Additionally, a new treatment is suggested based on the evidence and the theoretical understanding of phantom pain. This suggestion is operationalized in a quantitative project, which aim is to measure the effects of the suggested treatment. This will be done in **section 6.** Here it will also be discussed what the design can help illuminate in regards to phantom pain, and what it cannot. In **section 7**, the paradigm of the study suggested is tested with two pilots suffering from phantom pain. These results are presented and discussed. It is then evaluated whether the paradigm is feasible or

needs to be altered. In this section, aspects uncovered in the pilot study will also be tied to the mechanisms and theories accounted for earlier. **Section 8** will conclude the project, and in **section 9** reflections and finalizing thoughts will be made.

2. Perception

Perception allows us to interact with the world. Some molecules are perceived as odors, compressed air molecules, perceived as sound, different receptors throughout the body allows us to perceive touch, differentiate between hot and cold, etc. (Breedlove & Watson, 2013, p. 223). The current section does not seek to go into detail with every aspect of perception. The questions which will be treated in the current section are, how we detect touch and pain, and how pain distinguishes from other sensations. The aim of the current section is to lay the foundation of an understanding of how something as complex as pains and sensations in a missing limb can occur. The mechanisms behind phantom phenomena will be the topic of the next section.

Traditionally, perception has been distinguished in two ways, as being a passive and an active process (De Ridder et al. 2014; Lobanov, 2012). Passive perception is the idea that the brain passively absorbs sensory input, processes this information, and reacts with the appropriate motor and autonomic response (De Ridder et al., 2014, p. 6). In active perception on the other hand, the brain is not just passively absorbing sensory information, but can emphasize certain inputs it expects to be present or even create experiences in the absence of sensory inputs (ibid.). These views have been the content of discussion in classic studies conducted by among others Gibson and Bateson. Today, it is however the widespread conviction among cognitive scientists that perception is active. This is partly due to the fact that the idea of passive perception implicates that sensations such as touch or pain cannot be anticipated in the absence of stimulus. It is however a well-known fact, that anticipation of a painful stimuli can greatly exaggerate the pain-experience (Edwards et al., 2015; Vase et al., 2010; Sullivan, 2009; Melzack, 2001), and pain can even occur in the complete absence of stimulus, as for instance with chronic back-pain, phantom pain or during hypnosis (Oakley & Halligan, 2009; Derbyshire et al., 2004). Secondly, it implicates that the etiology of all pain must be peripheral. Even though phantom pain can be modulated by several peripheral factors, it cannot be solely explained by these. This is a point which will be treated further in **section 3.** Active perception, on the other hand, allows phenomena such as phantom pain to exist due to the fact that inputs are

not necessary to create experiences. The idea of higher cognitive functions which modulates lower in a top-down fashion will be treated in **section 4**.

The fact that it is the widespread conviction that perception is active is however far from a final conclusion. It primarily raises the question: How is perception active? For now, this discussion will be left but will be a returning topic in **section 5**.

2.1 Touch and pain

Touch can be considered a blend of many sensations (Breedlove & Watson, 2013, p. 235). Light touch is detected by four types of receptors: the Pacinian corpuscles, the Meissner's corpuscles, Merkel's discs and Ruffini's endings. The *Pacinian corpuscles* detects vibrations over 200 Hz. The *Meissner's corpuscles* responds to changes in stimuli and detects localized movement between skin and a surface, whereas *Merkel's discs* seem to be especially responsive to edges and to isolated points on a surface (ibid., p. 236). *Ruffini's endings*, detects stretching of the skin when fingers or limbs are moved. The sensation of touch is a mixture of inputs from these receptors. When the threshold has been reached the receptors sends the information along axons to the spinal cord where it enters the dorsal horn. It then travels along the dorsal column of white matter to the brainstem and synapse on the neurons in the medulla. Here the signal shifts contralaterally and ascends to the thalamus, from where it is directed to the primary somatosensory cortex (ibid, p. 238). Even though this process is largely directed in a bottom-up fashion, it is nevertheless influenced by top-down processes. This point will be treated further in **section 4.**

Even though pain is most often considered an unpleasant sensation, it is perhaps for that very reason an important marker to help avoid injury or rehabilitate from it. Dennis & Melzack (1983) argue that nearly all species have elaborate mechanisms which cope with events followed by damage to the skin or internal organs. These events might involve loss of blood, entry of toxins into the body or infection (Dennis & Melzack, 1983, p. 153). Some of these events may take time to heal and any activity which competes with the body's metabolic capacity might increase the probability of prolonged or additional injury (ibid.). In this sense, pain can help us in several ways: Immediate pain causes us to withdraw from the source, to avoid further injury;

Persisting pain-signals can change behavior such as sleep or feeding which can help promote recovery or avoid activity which might worsen the injury; Expression of pain serves as a social signal to others, eliciting care giving behavior from them (Dennis & Melzack 1983; Breedlove & Watson, 2013, p. 241). There are cases of individuals who have a congenital insensitivity to pain. These people tend to die at a young age, most likely due to the fact that they are incapable of sensing the warning signals coming from the body, and thereby less likely to recover from injury (Breedlove & Watson, 2013, p. 241).

Some receptors are specialized for pain and responds to noxious stimulations. These are called *nociceptors*. Nociceptors can be free nerve endings, which are specialized in detecting several painful stimuli, for instance transient receptor potential vanilloid type 1 (TRPV1) detecting heat or cool-menthol receptor 1 (CMR1) detecting coolness (ibid., pp. 243-244). When a noxious stimulus arrives from the peripheral nervous system (PNS) to the brain, it can lead to a painful experience. When pain is caused by factors from the external world like a burn, it excites free nerve endings that functions as nociceptors (ibid.). Action potentials are then generated in neurons in the PNS. The signal travels along the axon to the spine, where it enters the dorsal horn. Here the signal goes across the midline to the opposite side, where the signal begins to ascend to the brain along the anterolateral column of the spinal cord. The signal then reaches the thalamus, before it is distributed to the relevant locations in the cortex, like the cingulate cortex and somatosensory cortex (ibid., p. 245). This is a typical bottom-up process in which signals from the PNS go to the central nervous system (CNS) and is interpreted by higher brain functions as being painful. Pain is however much more complex than this traditional view of pain, due to the fact that higher brain functions - such as attention - can regulate how and to which degree the pain is perceived (ibid., p. 242). This is a point that will be further discussed in **section 4**.

Pain is a complex phenomenon which is not a simple question of painful stimulus. Neuropathic pain is an example of pain that is due to inappropriate signaling rather than tissue damage. This can be a part of chronic back pain as well as phantom pain (ibid., p. 246). In the case of neuropathic pain, amplification of the signal can take place in both the cortex and in the spinal cord. After peripheral injury, microglial cells release chemicals than can make the dorsal horn neurons hyperexcitable render-

ing them more prone to fire (Breedlove & Watson, 2013, p. 246; Flor, 2002). This can cause a flooding of the thalamus with erroneous signals (Flor, 2002). In case of chronic pain, the pain does not any longer serve as a warning signal of pathology, but has become the pathology itself.

Chronic and phantom pain can be considered quite special cases, due to the fact that the pain is not stimulus driven. In phantom pain, there are no somatic factors which can account for the pain that the patient is feeling. In this sense, pain perception is not simply to be considered a bottom-up process, but just as much influenced by top-down processes, in which higher brain functions influences lower. This point will be treated further in **section 4**.

It has been discussed whether pain is simply a variation of the same processes as sensations such as touch. A hard touch (pressure) seems to be able to elicit painful experiences so the question is: Is pain just another sense? At first glance it might seem plausible that this type of pain is simply a question of threshold of receptors. A light touch gradually becoming more powerful will at some point become painful for most healthy people. Pain however, distinguishes itself in several ways. First of all there are receptors specializing in detecting noxious information (nociceptors). Secondly, these nociceptors do not even share the same neural pathways to the brain. As already explained, sensory information shifts contralaterally in the brainstem, where pain information shifts contralaterally immediately as it enters the spinal cord. Furthermore, pain is also associated with anterior cingulate cortex, the thalamus, prefrontal and parietal cortices (Sullivan, 2009, p. 14; Wager et al., 2004). In this sense, pain is distinct from sensations such as touch, but they are nevertheless intrinsically intertwined. Sensations may modulate the experience of pain, but pain does not need originate from touch or any other external factors. This point will be central in **sections 4 and 5**.

To summarize, pain is largely an adaptive phenomenon which helps to protect an individual, but can in some cases become maladaptive. Chronic pain is an example of pain, which do not any longer serve as an indicator of a problem but becomes the problem itself. Pain in a missing limb hardly serves any protective purpose, so the question is how to make sense of it. In order to do this an understanding of the mech-

anisms involved in phantom pain is needed. This will be the topic of the next section, about the mechanisms involved in phantom pain.

3. Phantom limbs and the mechanism involved

In the current section, characteristics and mechanisms involved in phantom limbs will be investigated. The intention of the current section is to make an account of the mechanisms involved in phantom phenomena in particularly phantom pain, and how many aspects together constitutes the elusive phenomenon. This section will start with an account of the perhaps best understood phenomenon known in amputees, more specifically stump pain. Stump pain is not a phantom phenomenon but nevertheless a factor which affects many amputees and has an impact on phantom pain. Next, an account of phantom sensation will be made and finally phantom pain will be accounted for. During these accounts, interconnections between the phenomena will be discussed based on the findings of empirical studies. Even though phantom sensations and phantom pains are distinguished clinically they are closely related and may share many of the same mechanisms. This will be reflected in the current section with some overlapping in the accounts of the two phenomena.

3.1 Stump pain

Stump pain (pain in the residual limb) is a very common phenomenon in the acute phase after amputation (Nikolajsen, 2012, p. 3). After a period of recovery stump pain usually reduces, but it might in some cases persist. There can be a variety of reasons for these pains. Usually they are related to abnormal stump tissues, adherent scars, localized infection, or stump claudication (primarily in patients with vascular diseases or where an ischemic cause precipitated the amputation) (Kulkarni & Grady, 2010, p. 130). It might even be caused by allergic reactions to prosthetic materials. Neuropathic pain might however also contribute. In some cases, these pains are described like burning oil on the stump, or a sharp, cramping or stabbing sensation (ibid.). These pains may be constant or paroxysmal (a sudden outburst of pain), or can be both, where pain is always in the background but can suddenly increase in a pain attack (ibid.). Sensory abnormalities such as painful responses to normally nonpainful stimuli (*allodynia*) or a heightened pain response to painful stimuli

(*hyperalgesia*) (Nikolajsen, 2012, p. 3; Kulkarni & Grady, 2010, p. 131) can also be present in the stump. Neuropathic pain can occur when an insult to a nerve causes changes in the peripheral and central nervous system (Kulkarni & Grady, 2010, p. 130; Makin et al., 2015). Stump pain can be both nonspecific and in some cases be caused by a stump neuroma which has formed following amputation. In contrast to efferent nerves, afferent nerves have the capability of regrowing. When a limb has been amputated, the collateral sprouting happening in the residual stump can cause the nerves to get intertwined and form a knot called a neuroma**.** A neuroma can make the stump pressure sensitive and can lead to excruciating pain. The neuroma can also cause spontaneous firing which seems to be a result of the upregulation of sodium channels (Flor, 2002, p. 185). This seems mainly to be due to ectopia (neuronal discharge that is generated in the soma or along the axon) (ibid.).

Normally during a surgical amputation nerves are embedded, so that damage to the nerves is minimized. It is no guarantee that a neuroma will be prevented, but risks are decreased. In cases of traumatic amputation risks of formation of a neuroma might be increased (Nikolajsen, 2012, p. 3). Stump pain caused by neuromas can like phantom pain be hard to treat. This is due to the fact that surgically removing them is a new insult to the nerves, which can lead to the formation of a new neuroma. With surgical alteration of the stump there is also a risk of making matters worse (Kulkarni & Grady, 2010). Despite stump pain not being a phantom phenomenon it does correlate with phantom pain (Nikolajsen, 2012). Stump neuromas have even been hypothesized to be the cause of phantom pain. Phantom pain is however occasionally reported to be present immediately after amputation before a neuroma can have formed. Despite the fact that local anesthesia of the stump can alleviate phantom pain, this does not seem to be the case for all patients (Birbaumer et al., 1997). In this sense, stump neuromas cannot be the sole cause of phantom pain, but can nevertheless influence it. The topic of stump pain will be left for now, but will occasionally be referred to in the following sections.

3.2 Phantom sensation

Ribbers et al. (1989) defined a phantom as being the "*continuous awareness of a (or part of a) non-existing or deafferented body part with specific for, weight, or range of motion"*. Phantom sensation refers to painless sensations of a phantom, like experiences of shape, length, posture and movement (Nikolajsen, 2012, p. 1). For some amputees the phantom might suddenly move autonomously and get stuck in a position, while other amputees can control the movements of the phantom (Richardson, 2010, p. 138). It could be tempting to prescribe these sensations as being due to memories of the limb (Flor, 2002). Memories have been illustrated to have an impact on phantom sensations (Flor, 2002; Nikolajsen, 2012). Phantom sensation do not even have to reflect the limb itself, but can also include sensations of the limb being clothed or a watch being present on the phantom wrist (Katz & Melzack. 1990 in: Richardson, 2010, p. 138; Wesolowski & Lema, 1993 in: Richardson, 2010, p. 138), further supporting the idea of memories playing a role. Phantom sensations have however also been reported by individuals with congenitally absent limbs, (Brugger et al., 2000; Saadah & Melzack, 1994) which illustrates that memories cannot be isolated as the single cause, since congenital amputees have never had experiences with sensation in the limb. One might speculate that memories might not be the cause of phantom pain but can modulate and define the otherwise occurring phantom experience. Furthermore, phantom sensations are not confined to the physical limitations of the limbs**.** There have been reports of many bizarre phenomena as illustrated in the following **figure 3.2a**.

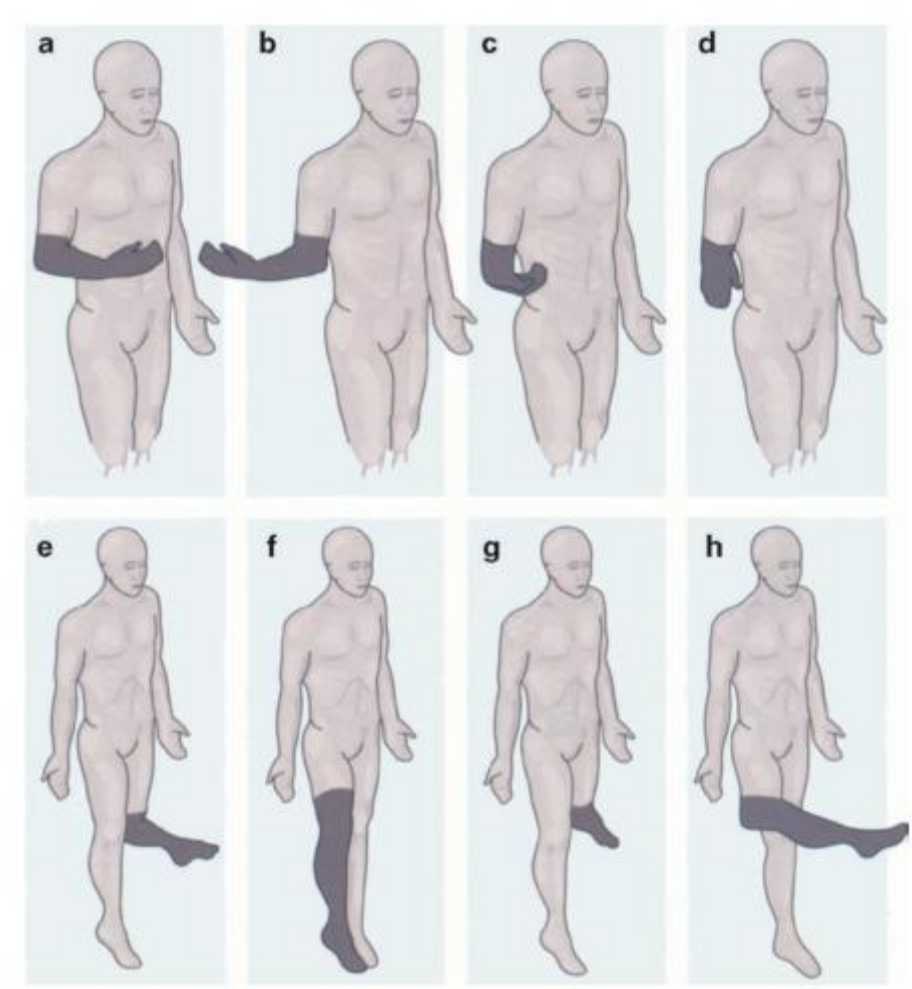


Figure 3.2a (From Fig. 10.1 in: Richardson, 2010 p. 139):
Different sensations in limb amputees. Shadow area represents the phantom. Pictures a-d are of upper limbs, e-h of lower limbs.

A phantom limb can for instance be fixed in a position (pictures a and f). Phantom limbs can also be in unusual positions (picture b) or even impossible positions (pictures e and h). In this sense, phantom limbs can take positions in relation to the body otherwise impossible for an actual limb. This might as Ramachandran & Rogers-Ramachandran (1996) suggested, be due to a lack of visual input. Proprioception lets us know where our body parts are located at any given time, but it is possible, that it requires occasional feedback from for instance the visual or other systems to help calibration. It might be, that this lack of input confuses the proprioception of the amputated limb and can cause some of the sensations depicted in the **figure 3.2a.** In the study of Ramachandran & Rogers-Ramachandran (1996), four out of the five partici-

pants experiencing ‘clenching spasms’ in the phantom hand were capable of relieving this pain by opening both hands while using a mirror box (Ramachandran & Rogers-Ramachandram, 1996, p. 379). However, as already mentioned in the introduction, burning and lancinating pains remained completely unaffected by the procedure, indicating that even though visual feedback was capable of influencing the phantom phenomena and give pain relief to some extent it was not tapping into a primary mechanism of the phenomenon.

Another phenomenon reported by approximately 30% of amputees is a feeling of telescoping in which the phantom retracts into the residual limbs (Flor, 2002, p. 183) (pictures c, d, e and g). In some instances the phantom telescopes so far that the digits are at the end or inside the residual limb (Richardson, 2010, p. 138). This telescoping might also be accompanied by a shrinking of the phantom (Flor, 2002, p. 183). An earlier hypothesis has been that phantom pain reduces as telescoping progresses (Katz, 1992), however Montoya et al. (1997) and Richardson et al. (2006) did not find any such relation. Some even suggest that phantom pain and telescoping are positively related - in other words, the higher degree of telescoping the more pain (Grüsser et al., 2001; Montoya et al, 1997).

Phantom pain and phantom sensations are also strongly correlated. In Kooijmann et al. (2000), phantom pain was present in 36 out of 37 amputees experiencing phantom sensations but only in 1 out of 17 with no phantom sensations.

3.3 Phantom pain

Phantom pain (pain in the missing limb) often debuts in the first week after amputation, peaks in the first couple of months, and then usually diminishes. For 5-10% of these patients however, severe phantom pain persists (Nikolajsen, 2012, p. 1). The causes of amputation vary from country to country. In developing countries trauma is the main cause of amputation, due to inadequately treated fractures, motor vehicle accidents, etc.; in countries with recent warfare or civil unrest, trauma accounts for 80% of all amputations (Esquenazi, 2004, p. 831). In developed countries such as the US, Japan and Denmark, 68% of all amputations are caused by disease, such as vas-

cular complications of diabetes and tumor, whereas trauma accounts for approximately 30% (ibid.).

As mentioned in the introduction, phantom pains often have some distinct features described by the amputees. These involve sensations of burning, cramping, crushing, lancinating, shooting, stabbing, boring, squeezing or throbbing (Ramachandran & Altschuler, 2009; Flor, 2002; Nikolajsen & Jensen, 2001). A study conducted by Jensen and colleagues (1985) provides empirical data of how often these words are used by amputees to describe their phantom pain. Jensen et al. (1985) provides a more nuanced list of words. See **table 3.3a.**

Table 3.3a: *(Table V in Jensen et al., 1985, p. 273)*
Words used to describe phantom pain by amputees 8 days (n=42), 6 months (n=33) and 2 years (n=20) after amputation. Data are presented as percentages of patients.

Pain character	8 days	6 months	2 years
Knifelike	55	27	20
Sticking	36	9	10
Shooting	14	9	0
Pricking	14	6	5
Burning	14	45	65
Squeezing	10	52	30
Throbbing	7	12	5
Pressing	7	0	0
Cramplike	5	3	0
Sawing	5	3	0
Dull	5	3	5
Freezing	0	6	0
Crushing	0	6	15
Other	7	6	0

The fact that different words are used to describe the pains illustrates that phantom pain can be experienced rather differently between individuals. Basically phantom pain can take form of all kinds of different painful sensations. One might speculate that the use of these different words is an expression of the pain being constituted by several mechanisms in different proportions among amputees, leading to different painful sensations. Additionally, factors such as distress, coughing, urination and manipulation of the stump, seem to play a role in the modulation of phantom pain (Nikolajsen 2012, p. 3), indicating that both peripheral and central mechanisms are

involved. Peripheral and central mechanisms will be described in the following sections.

3.3.1 Peripheral and central mechanisms in phantom pain.

Despite phantom pain being a thoroughly investigated area, still little is known about it (Nikolajsen, 2012; Birbaumer et al., 1997; Ribbers et al, 1989). A variety of factors have been found to play a role in phantom pain. Following an amputation a series of peripheral and central changes occur (Makin et al., 2015; Nikolajsen, 2012; Nikolajsen & Jensen, 2001). First an account of the peripheral mechanisms which has been found to be involved in phantom pain will be made and discussed. Then the central mechanisms which involve both changes in the spine and brain will be discussed.

3.3.1.1 Peripheral mechanisms

From observations in the literature it seems that mechanisms in the periphery are involved in phantom pain. One argument is that phantom pain has been found to be more frequent in amputees with long-term stump pain (Desmond & MacLachlan, 2010; Kooijman et al., 2000). Katz (1992) found a correlation between temperature of the stump and phantom pain. As Nikolajsen (2012) points out, it is not clear whether this difference in temperature represents a pain-generating mechanism or is a result of pain (p. 11). It might be that lower temperature in the stump is an expression of reduced near-surface blood flow, which has been shown to correlate with burning phantom limb pain (Sherman & Bruno, 1987 in: Flor, 2002, p. 182). This is often the case in amputees with dysvascular disorders, like the patients recruited in Katz (1992).

Pressure sensitive neuromas have also been demonstrated to exacerbate phantom pain (Nyström & Hagbarth, 1981), which can for instance be caused by ectopic dis-

charge. Ectopic discharge might however not only occur in the stump, but also in the dorsal root ganglion, amplifying signals coming from the stump (Flor, 2002, p. 185).

Sherman & Sherman (1983) found that neuropathic stump pain is present in 61% with phantom pain and in 39% without phantom pain (Sherman & Sherman, 1983 in: Kulkarni & Gradi, 2010, p. 130). In addition regional anesthesia has been illustrated to reduce phantom pain (Birbaumer et al., 1997). This study will be accounted for shortly. Some have even reported regional anesthesia to actually evoke phantom pain (Paqueron et al, 2004; Martin et al, 2003). Despite several peripheral aspects can be linked to phantom pain, none need to be present for phantom pain to occur.

3.3.1.2 Central mechanisms

One of the central mechanisms that seem to play a role in phantom pain is sensitization in the dorsal horn, where an increased activity of peripheral nociceptors has led to a permanent change in the synaptic structure. This can cause an increased excitability and a reduction of inhibitory processes, making the neurons more prone to fire (Flor, 2002, p. 183). Flor (2002) hypothesizes that a possible mechanism in phantom pain is that low threshold afferents become functionally connected to ascending spinal projection neurons responsible for carrying nociceptive information (ibid.). Low threshold input would then be able to activate normally high threshold projections causing the signal to be interpreted by the brain as being painful.

Aydin and colleagues (2005) reported a case of a 65 year old woman who had suffered from phantom pain since the age of 5. Her phantom pain diminished progressively in parallel with the growth of an intraspinal tumor. After the removal of the tumor phantom pain gradually reappeared over three months. Spinal anesthesia has also been found to have an impact on the development of phantom pain (Tessler & Kleiman, 1994). The evidence is however sparse, and the effects of spinal anesthesia in already established phantom pain, has only been found to be effective in very few instances (Moura et al., 2012).

Clinical observations suggest that cortical structures are involved, due to the fact of the share complexity of phantom pain. For instance, phantom pain is sometimes similar to the pain experienced by the individual before amputation (Flor, 2002), and

anesthesia is not always effective (Moura et al., 2012; Birbaumer et al, 1997; Paqueron et al, 2004; Martin et al, 2003). The fact that there is a relation between cognitive-emotional aspects such as catastrophizing and phantom pain (Vase et al. 2011) serves to illustrate the point, that there is more to phantom pain than peripheral and spinal mechanisms. Furthermore, phantom pain is known to be primarily localized to the distal parts of the missing limb. In other words, the pain is often located in the fingers and palms of upper limb amputees and in the toes, feet and ankles in lower limb amputees (Nikolajsen, 2012, p. 3). Nikolajsen (2012) hypothesized that the larger cortical representation of the distal limbs as opposed to the smaller representation of the proximal might play a role in this.

Flor et al. (1995) reported a high correlation between cortical reorganization and phantom pain ($r = 0.93$) (p. 482). After amputation the cortical representation of the limb shrinks and the adjacent area expands (Ramachandran & Rogers-Ramachandran, 1996; Flor et al., 1995; Flor 2003). A reorganization of the somatosensory cortex occurs (S1), which is also influenced by abnormal changes in the dorsal root, dorsal horn and random input from stump neuroma (Flor, 2002). One might speculate this is why neuropathic pain in the stump shares a correlation with phantom pain. Flor et al. (1995) suggested that phantom limb pain only develops if the relevant portion of S1 reorganizes and becomes responsive to alternate input, for instance from a neuroma. In addition, a reorganization of the primary motor cortex (M1) occurs in most amputees (Sumitani, 2012, pp. 337-338).

One might speculate that cortical reorganization affects the phenomenon of telescoping. Perhaps the larger representation of the distal extremities such as hands or feet are more intact following cortical reorganization compared to the proximal such as arms or legs. This could explain the occurrence of telescoping.

In a study by Birbaumer and colleagues (1997) the relationship between cortical reorganization and phantom pain was investigated. In their study they included six patients with phantom limb pain and four pain-free amputees as controls. After brachial plexus blockade three of the six patients with phantom pain experienced an elimination of the pain (mean change = 3.8 on an 11-point scale; $Z = -1.83$; $p < 0.05$) (ibid.). It is interesting that after a procedure temporally eliminating all sensation and movement of the limb, only half experienced pain reduction. Even more interesting

is the fact that for the three patients experiencing alleviation a very rapid reduction of cortical reorganization in the somatosensory cortex was observed (change = 19.8mm; $t = 5.60; p < 0.05$), whereas for the three patients not experiencing pain relief cortical reorganization remained virtually unchanged (mean change = 1.6mm). This evidence illustrates that peripheral aspects can have an influence on phantom pain, but not in all cases. It also indicates that cortical reorganization can potentially be causally linked to phantom pain.

Before continuing to other central mechanisms involved in phantom pain, a few reflections should be made about cortical reorganization. One question which seems to be central is whether there are different kinds of cortical reorganization. Reorganization can occur slowly through long-term potentiation and collateral sprouting following amputation, but it can also be observed rapidly following anesthesia, as illustrated by Birbaumer et al. (1997) which shows the reorganization taking place 20 minutes after injection. Furthermore, psychological trauma is an example of conditioning taking place in the absence of long-term potentiation. In this sense, it could be tempting to distinguish between a "slow and physical" reorganization and an "immediate and functional". However, this division is problematic due to the fact that even in cases of temporary reorganization there can be physical changes such as neurochemical changes. It is not yet known which forms of reorganization are related to which changes in function, behavior or experiences. However, it does seem that not all types of physical reorganization are a precondition for a functional change.

Top-down processes like attention, depression or pain catastrophizing (Sullivan, 2009; Vase et al., 2011) can likewise have an impact on the severity of phantom pain. Even though the mechanisms underlying phantom pain have not yet been clarified, it seems that both the peripheral and the central nervous system play a role (Nikolajsen & Jensen, 2001, p. 110; Flor, 2002, p. 182).

Ramachandran & Altschuler (2009) speculate that there are at least five possible origins to phantom pain: 1) Irritation of nerve endings (neuromas) in the amputation stump; 2) Central remapping can lead to the possibility of low threshold touch input to cross-activate high threshold pain neurons; 3) the remapping itself can lead to an output which might be interpreted as pain in higher brain centers; 4) The missing visual and proprioceptive input that a motor command has been executed might be

perceived as pain; 5) Preamputation pain tend to persist as a memory in the phantom (Ramachandran & Altschuler, 2009, p. 1696). Flor (2002) suggested that phantom limb pain is due to memorized pain, which has occurred due to long-lasting noxious input to the limb. Long-lasting noxious input to the limb leads to development of a cortical pain memory. Even though a significant relation has been found between preamputation pain and phantom pain, the relationship is far more complex (Nikolajsen, 2012, p. 7). In Nikolajsen (2012), 56 patients scheduled for lower-limb amputation were asked about pain before the amputation, after 1 week, 3 and 6 months. Phantom pain was more frequent after 1 week, but not after 6 months in patients who had moderate to severe preamputation pain (VAS[1] > 20) compared to patients with less preamputation pain. In addition, some patients with severe preamputation pain never developed phantom pain, while others with only minimal preamputation pain developed severe phantom pain (ibid.). Another limitation to the theory is that it does not account for cases where phantom limb pain is present in adults with congenitally absent limbs (e.g. Brugger et al., 2000; Saadah & Melzack, 1994). The theory can however help explain the fact that phantom pain can mimic preamputation pain in both character and site (Kulkarni & Grady, 2010, p. 132).

The cortical reorganization after amputation illustrates the complexity of the mechanisms behind phantom pain. It is not known whether cortical reorganization is a driving mechanism behind phantom pain, but it seems that there is a strong correlation between them. MacIver et al. (2008) hypothesized that it was possible by the use of mental imagery to provide sufficient stimulation to the deafferented areas, thus reducing the cortical reorganization and thereby reduce pain. MacIver et al. (2008) found a reduction in the cortical reorganization and in the measures of pain intensity and unpleasantness after an intervention comprised of mental imagery of sensation and movement of the phantom limb. The fact that a top-down process like mentally training a phantom limb, can decrease cortical reorganization and reduce phantom pain, serves to illustrate the importance of central mechanisms in phantom pain as well as the influence of top-down processes. The study of MacIver et al. (2008) will be described in more detail in **section 4**.

[1] Visual Analogue Scale

Even though phantom pain can occur without input from the periphery, both peripheral and central aspects seem to interact. Peripheral factors might greatly increase central reorganization. In this sense the eradicate firing of neurons in the neuroma creating a noise-like input, might increase central map reorganization (Spitzer et al., 1995). Peripheral factors cannot be the primary factor in phantom pain though, due to the fact that phantom pain also occurs in cases with no pathology in the periphery. It seems evident that cortical reorganization needs to have taken place for phantom pain to occur (Flor et al., 1995; Richardson, 2010, p. 142). Whether the interaction between the peripheral and central aspects and to which extent they are expressions or causes of phantom pain is still largely discussed.

To summarize it seems that both peripheral and central aspects are involved in phantom pain. Evidence of the peripheral aspects is that stump manipulation can exacerbate phantom pain and the fact that prevalence of stump pain correlates with phantom pain. The fact that phantom pain can occur even in the absence of stump pain serve to illustrate that phantom limbs do not originate as a figment of stump pain. The correlation might just illustrate that stump pain has a modulating effect on phantom pain. Central aspects seen in relation to phantom pain are: sensitization of the dorsal horns, reorganization of the primary somatosensory cortex and phantom pain as a pain memory. Sensitization of the dorsal horns still requires input for pain to occur, and despite cortical reorganization correlates strongly with phantom pain it is still unknown whether and how pain originates from it. Some suggestions have been made and will be accounted for in the following section. Phantom pain as a pain memory requires the individuals to have a memory of pain in the missing limb, which does not explain phantom pain in amputees with congenitally absent limbs (Brugger et al., 2000; Saadah & Melzack, 1994). As described in this section several factors have been demonstrated to play a role in phantom pain, but none have redeemed the status of being the sole cause of it. Due to the fact that phantom pain seem to be able to occur in the absence of peripheral, but not in the absence of central serves to illustrate the importance of central mechanisms. The next section will therefore seek to uncover top-down processes and their influence of phantom pain.

4. Top-down processes

As already mentioned in the former section, top-down processes seem to play an important role in phantom phenomena. In the current section these processes will be further explored in relation to phantom pain. Top-down and bottom-up processes are often defined as being opposites but in reality they are complexly intertwined. Painful experiences are products of a complex interaction between higher and lower brain functions as well as input from the periphery (Melzack, 2001). More specifically how that is will be described further in **section 5.** In this sense, top-down and bottom-up processes are to a higher extent to be considered abstractions than distinct processes. The current section will seek to account for top-down processes and also illustrate the complexity of phantom pain and how pain can be modulated by thought processes and states of mind.

As already accounted for in **section 2**, pain is not a passive system which transmits noxious information to the brain in a bottom-up fashion as once believed, but also altered by expectation, attention and the emotional state of the individual in a top-down fashion (Lobanov, 2012, p. 3). Bottom-up processes refers to processes in which signals from lower-order mechanisms, such as sensory input, travels to the brain where it is processed by higher-order mechanisms like the thalamus and cortex (Breedlove & Watson, 2013, pp. 231, 570). Top-down refers to processes in which a processing in the higher brain areas modulates sensory information from lower order mechanisms. Here some signals can be suppressed while others amplified (ibid., p. 570).

Kosslyn and colleagues (2000) illustrated that color perception can in fact be altered through top-down processes. Eight highly hypnotizable participants were asked to observe a color pattern in color, a gray-scale pattern in color, a color pattern as a gray-scale and a gray-scale pattern in gray scale. Brain regions involved in perception of color in the fusiform and lingual region was identified with positron emission tomography (PET) by analyzing the results of when subjects were asked to perceive color as color, and gray-scale as gray scale (Kosslyn et al., 2000, p. 1279). During hypnosis, these areas had an increase in activation when asked to perceive color regardless of the actual stimulus. Likewise the brain regions decreased activation when they were suggested to see gray scale, regardless of stimulus (ibid.). In this sense,

hypnosis works as a top-down regulation. Higher brain areas involved in the conscious processing of suggested elements are transformed into a modulation of sensory input. This will be a returning point later in the current section.

Top-down processes also seem to have a large effect on pain, since pain can be significantly worsened or alleviated by higher-order mechanisms. Maintaining attention to pain can for instance exacerbate it (Sullivan, 2009, p. 13.), in fact expectation of chronic pain may be even more disabling than the pain itself (Lobanov, 2012, p. 4). A factor which is known to significantly worsen pain is pain catastrophizing. *Pain catastrophizing* is defined as "*an exaggerated negative mental set, brought to bear during actual or anticipated painful experiences."* (Sullivan et al., 2001 in: Sullivan, 2009, p. 4).

Catastrophizing contributes to heightened levels of pain and emotional distress and increases the probability of an extended time with pain (Sullivan, 2009, p. 7). Pain catastrophizing can be considered from different perspectives. One way is to consider it a cognitive error, which should be treated by cognitive restructuring to reduce dysfunctional thinking (Beckian model of depression) (Sullivan, 2009, p. 9). Another perspective sees catastrophizing as an evaluating process, due to expectations of heightened pain, as well as heightened attention to pain (ibid., p. 9). Some perspectives even see pain catastrophizing as an evaluating process, where the individual employs catastrophizing in an effort to garner social support from others (ibid., p. 10). Regardless of the perspective one takes on pain catastrophizing, it is a maladaptive process which can significantly worsen the state of pain.

A distributed network of brain regions have been found to have an increase in activation during focused attention to pain, among others the prefrontal and parietal cortices, the thalamus and parts of the anterior cingulate cortex (Sullivan, 2009, p. 14; Wager et al., 2004). High pain catastrophizers tend to show significantly more activation in these areas during painful stimulation than low pain catastrophizers (ibid.). More specifically these areas are the dorsolateral prefrontal, the anterior cingulate and the inferior parietal cortex (ibid.). Sullivan - the inventor of the pain catastrophizing scale, a measurement of pain catastrophizing which will be accounted for later in **section 6** - argues that attentional mechanisms might at least partly account for the relation between catastrophizing and the experience of pain. Sullivan

hypothesized that a reduction in pain catastrophizing will decrease the risk of the persistence of pain and disability (Sullivan, 2009, pp. 7-8).

It should here be noted, that whether there is a causal connection between phantom pain and pain catastrophizing is unknown. So it could be argued that an individual being prone to catastrophizing is not necessarily at higher risk of getting phantom pain. It might be that phantom pain increases pain catastrophizing. Nevertheless, the fact that there is a correlation (Vase et al., 2011) leads one to speculate, that a reduction in catastrophizing might decrease the phantom pain, and vice versa.

In a study by Lorenz et al. (2005) it was investigated how expectancy of painful stimuli can affect the evaluation of the intensity of the pain. In their study two different pain intensities (high and low) were administered to the participants and cued by different tones. When an invalid cue had been given, low-intensity stimuli were perceived as more painful whereas high-intensity stimuli were perceived as less painful. Brown et al. (2008) supplemented this finding by including at third pain intensity (medium) as well as certainty as a parameter. In their study the participants were given visual cues regarding the pain intensity (low, medium, high or unknown). When the forthcoming stimulus was unknown, high intensity stimuli were perceived as less painful, medium intensity stimuli were perceived as less painful, and low intensity stimuli were perceived as more painful compared to certain expectation (Brown et al., 2008, p. 243). These findings illustrates that expectations of painful stimuli can increase the actual experience.

As formerly mentioned top-down processes can also serve to reduce pain. One of these effects is ironically one of the most pervasive in scientific studies and often sought to be eliminated when trying to investigate the effects of a drug or therapy. Despite the fact that it is an effect which has repeatedly shown to have a large impact on pain (Ramachandran & Altschuler, 2009, p. 1694), it is quite an elusive effect to harness on purpose. It is of course the placebo-effect. *Placebo* refers to a treatment or drug that has no direct physiological effect, but nevertheless alleviates pain (Breedlove & Watson, 2013, p. 250). In other words, placebo can be said to purely retain its analgesic effects from the individual's conviction. Despite the fact that pain is notoriously known to be highly susceptible to the placebo-effect, it is not everyone who is capable of experiencing pain relief (Ramachandran & Altschuler, 2009, p. 1694;

Wager et al., 2004). In the individuals who do experience pain relief due to placebo, has been shown via functional brain imaging to have a reduced activity in neural regions responding to pain, such as the spinal cord, cingulate cortex, insula and thalamus (Wager et al., 2004). Greater activation in regions with opioid receptors can likewise be observed (Breedlove & Watson, 2013, p. 250) suggesting that the effects of placebo might be related to a connection with the endogenous opioids, as endorphins. This can be an effect pervading studies trying to investigate the effect of a treatment, because a potential pain reduction might be caused by the fact that the individual believes it to be effective and not due to anything related to the treatment itself. The individual's conviction might cause a release of endogenous opioids resulting in pain alleviation, which could be wrongly attributed to the treatment. Of course, most studies control for this effect, but that is a topic for **section 6**.

Since the effects of placebo can be difficult to harness, other top-down-processes have often been the target in minimizing pain. One of these has been to disengage attention from pain. Probably all have experienced how a painful cut can easily be forgotten by doing something else and not think about it. However, as soon as you are reminded it might start to hurt again. This is true for most minor injuries, but diverting attention might get harder as sensation of pain increases. Attention is in this sense a very important factor, but it is mainly an immediate effect. A small injury as mentioned in the example rarely poses a problem. It heals and the pain completely disappears and often forgotten. Pain such as phantom pain or chronic back pain are however much more severe. The method of disengaging attention to pain can be seen in the studies of Hilgard (1967, 1971) and Oakley et al. (2002). In the former studies, hypnosis was used to reduce pain during the cold pressor, and in the latter, hypnosis was used to reduce phantom pain. The latter study will be accounted for in **section 6**. Diverting attention can be a coping strategy to reduce pain and is in essence a top-down process.

Ramachandran & Rogers-Ramachandran (1996), as accounted for in the introduction, used a different kind of top-down process to regulate pain - visual feedback. This was done to give amputees the impression that their phantom hand could move, and thereby change the sensation of the hand being stuck in an uncomfortable position. MacIver et al. (2008) used sensory and motor training of the phantom with mental imagery to facilitate a cortical reorganization. The study of MacIver et al.

(2008) illustrates that training a phantom limb with mental imagery alone could reduce phantom pain. The fact that mental imagery can have an impact on pain, serves to illustrate the effects of top-down processes. Mental imagery of movement and sensation has been demonstrated to activate motor and sensory cortices, even without physical stimulation or movement (Flor et al., 2006; Oakley & Halligan. 2009). MacIver and colleagues hypothesized that if trained it would provide sufficient stimulation to the deafferented neurons and thereby potentially reduce cortical reorganization (MacIver et al., 2008, p.2182). Additionally, they hypothesized that since cortical reorganization and phantom pain has been shown to strongly correlate (r=0.93) (Flor et al., 1995, p.482), a reduction in phantom pain would occur if there was a reduction in cortical reorganization (MacIver et al., 2008, p. 2182). In their study 13 participants (2 females) suffering from phantom pain were included (ibid.). The time since amputations ranged from 3-51 years (m: 24.54 years; SD: 17.1). The treatments consisted of a body-scan exercise followed by mental imagery. The participants were to imagine movement and sensations in the phantom limb (ibid., p. 2183). More specifically, the participants were encouraged to relax and focus on sensations from each part of the phantom (fingers, forearm, whether the limb felt warm or cool, etc). At the end the therapy (six sessions between 6-12 weeks and daily exercises), significant reductions were found in constant pain intensity ($p < 0.0005$) and in constant pain unpleasantness($p < 0.01$), as well as in the intensity ($p < 0.005$) and unpleasantness ($p < 0.03$) in daily pain attacks (ibid. p. 2185). Effect sizes were calculated by MacIver et al. (2008). Due to the fact that effect sizes often illustrates more about the effect of the therapy, the author of the current project has calculated the effect sizes achieved in MacIver et al., and presented them in **table 4a**.

Table 4a. *Effect sizes of the intervention on the different modalities of phantom pain calculated from the data in MacIver et al. (2008).*

MacIver, Lloyed, Kelly, Roberts and Nurmikko (2008)		Effect sizes in Cohen's d from pre to post therapy.
Constant pain	Intensity	*1.34*
	Unpleasantness	*0.88*
Exacerbations of pain (pain attacks)	Intensity	*1.00*
	Unpleasantness	*1.28*

The effect-sizes presented in cohen's d are large from pre to post therapy in all measures of phantom pain conducted. In other words, a substantial reduction in phantom pain occurred after the therapy had been administered.

It should here be noted that MacIver et al. (2008) did not compare these results to a control group, thus not capable of concluding that the reduction of phantom pain was in fact due to the therapy administered, or other factors of the therapy, such as placebo, relaxation, etc. However, if the reduction of phantom pain reported is in fact due to mental imagery, it would further support that top-down processes are important in regards to phantom pain.

As already mentioned hypnosis has been illustrated to be able to modulate color perception and pain. However hypnosis has not only been able to modulate pain by simple diverting attention. Like mental imagery of movement and sensation has been demonstrated to activate motor and sensory cortices without physical stimulation or movement (Flor et al., 2006), so has hypnosis (Oakley & Halligan, 2009; Derbyshire et al, 2004). Hypnosis can be defined as:

> "*… a process in which one person, designated the hypnotist, offers suggestions to another person, designated the subject, for imaginative experiences entailing alterations in perception, memory and action.*" (Kihlstrom, 2012, p. 21).

Despite similarities with mental imagery, they differ substantially. For instance, a suggested touch during hypnosis which is successfully imagined by the subject is

ideally attributed to the external world (perceived as being real), whereas an imagined touch is attributed to the imagination itself (Barnier et al., 2012, p. 156). In this sense, hypnosis can potentially enhance the vividness of internally generated experiences compared to mental imagery.

The current section has illustrated that top-down processes have a large influence on pain. Top-down processes can both exacerbate and alleviate pain. Maintaining attention to pain, or catastrophic thinking in regards to an injury can make a painful experience worse. On the other hand, effects such as placebo show that analgesic effects can occur solely from an individual's conviction. Diverting attention to pain can have a temporary effect, and in phantom pain providing visual feedback of the missing limb can ease clenching spasms, despite no effects have been shown in other painful sensations. Furthermore, and internally generated intervention (mental imagery of training a limb) has been illustrated to reduce phantom pain. The effects of hypnosis have likewise been used to illustrate the effects of top-down processes, and it was argued that the use of hypnosis might enhance vividness of mental imagery, rendering it an even more capable tool for regulating pain in a top-down fashion. The next section will consult the theories around pain and phantom pain to uncover why top-down processes seem to have such a large impact, as well as why treatment involving top-down processes generally seem to be more successful in the treatment of phantom pain.

5. Theory

In the current section theories revolving around perception and pain will be used to account for the phantom pain phenomenon, mainly the perspectives of predictive coding and Melzack's neuromatrix theory. The theories already accounted for will be briefly summarized. Limitation and forces will be discussed as well as the implications they have on phantom pain. Afterwards this leads to a general discussion of neuroplasticity - the neurological foundation of cortical reorganization. The hypotheses put forward by Ramachandran & Altschuler (2009) will be briefly discussed as well as how these can potentially be empirically tested.

5.1 Predictive coding

As already treated in **section 2** about perception being active, predictive coding offers the perhaps most radical approach. It can also help explain how phantom phenomena might exist. Before accounting for the theory it should be noted that predictive coding is largely a mathematical model, but since the current project only wish to illustrate the theoretical aspect of top-down processes, the mathematical aspect of the theory will not be accounted for.

According to Karl Friston, in predictive coding the brain can be considered a probability machine that constantly tries to make predictions about the world depending on previous experiences (Friston, 2012; Friston & Kiebel, 2009). In contrast to passive perception, where the brain sits idle by waiting for stimulus to arrive, the bayesian brain constantly makes predictions from which it synthesizes an internal model of the world. It then compares this internal model with sensory data. It is the deviation between the internal model and the sensory data - also called *prediction error* - which is feed-forwarded to higher brain areas. The internal model is then updated to reduce *uncertainty* (or *free energy* in predictive coding terminology) to make better future predictions (Friston, 2012). The ability to make reliable predictions is an essential mechanism for survival (De Ridder et al., 2012). This also implicates that sensory data which has already been predicted is irrelevant for the higher brain areas and therefore not feed-forwarded to conscious processing. In other words, it is not worth

the energy required for conscious processing, if higher brain functions have already predicted the sensory information, since it has not increased uncertainty in the system. In short, the brain seeks to decrease uncertainty. This is the basic assumption in predictive coding. In predictive coding, everything perceived is regulated by top-down processes and bottom-up processes only serve to pass along information that is to be compared with the internal model, and feed-forward what has not been predicted. All perception can be said to be biased.

Figure 5.1a illustrates how predictive coding explains how different hypotheses can be generated by the internal model about the same ambiguous stimulus.

Figure 5.1a. *The figure consists of a row and a column with the ambiguous symbol in the middle. When reading the row (A-B-C) the ambiguous symbol is most likely to be read as B. When reading the column (12-13-14) the ambiguous symbol is most likely to be read as 13. In predictive coding this is due to the top-down hypothesis which is being primed to win by the preceding flurry of sensory information. When you read the A, your B-hypothesis is being primed to win, and when you read the 12 your 13-hypothesis is being primed to win. So based on the context the brain forms an internal model inferred to be the most probable.*

In contrast to the simplified two levels in f**igure 5.1a**, there are a multitude of levels in the brain. In this sense the brain can be said to make predictions about the incoming flow of sensory information based on knowledge that has been acquired by trying to make prediction about the incoming flow of sensory information.

The current example only illustrated this point to be the case with visual information. It can however be questioned whether predictive coding apply to other senses or if it is reserved for visual inputs only. De Ridder et al. (2012) argue how phantom pain can be understood in a predictive coding perspective. Following amputation, a topographically specific prediction error based on temporal incongruity is produced (De Ridder et al, 2012). This is due to the fact that the input expected based on information in the memory is inconsistent with the sensory input, so an update of the internal model is necessary. There are more prediction errors occurring since the brain does not receive the same amount of information. As already mentioned unpredicted percepts are difficult to ignore, since it is important for survival. Predictive coding does however not really seem to predict why and how this update of the internal model results in the sensation of pain, and why the phantom sensations emerge. It does however illustrate that pain can be maintained, if it is constantly expected due to the superior role of top-down processes.

Büchel et al. (2014) argue that the prediction in predictive coding carries both the content of sensory input and its context, so it could be speculated that if the pain is always expected in every context, but the uncertainty of input is still increased, it might result in the filling in of a phantom to explain the expected pain. This still does not answer how the pain emerges to begin with however.

De Ridder et al. (2012) argue that phantom phenomena can be accounted for by predictive coding. De Ridder et al. (2012) explain that when a limb has been amputated it induces a topographically specific prediction error based on temporal and spatial incongruity in the part of cortex that has been deafferented. This will be referred to as the "missing limb cortex". When the missing limb cortex has been deafferented the adjacent areas will start to reorganize. When an individual is simultaneously under stress there is an increased activation in insula and anterior cingulate cortex as well as the missing limb cortex. The anterior cingulate cortex is associated with salience, so the activation of the missing limb cortex will be interpreted by the consciousness as being an actual limb. In this argument, an initial non painful reorganization becomes painful during hyperactivity of the missing limb cortex and anterior cingulate cortex when the individual is under stress.

Even though this argument offers something other theories of phantom pain do not - an account of the origin of phantom phenomena - it is rather speculative, with a lot of assumptions built into it. An issue with this argument is that it does not explain the correlation between cortical reorganization and phantom pain found by a substantial amount of literature (e.g. Flor et al., 1995; Ramachandran & Rogers-Ramachandran, 1996; Flor 2003; MacIver et al., 2008; Birbaumer et al., 1997; etc.). If it is a necessity that an individual is under stress in order to experience phantom pain, it would be expected to observe more people without phantom pain who has a high degree of cortical reorganization. This however, seems not to be the case.

A different approach to understand phantom pain is Melzack's neuromatrix theory of pain.

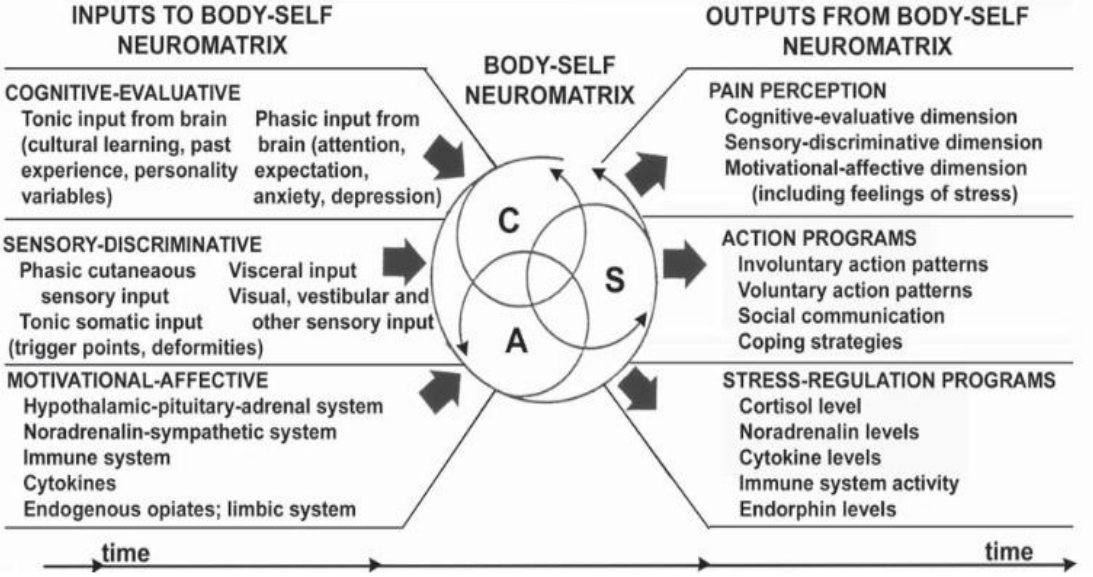
5.2 Neuromatrix theory of pain

The neuromatrix theory of pain gave a different understanding of how pain works. Pain is far from the simple Cartesian view in which pain is solely a sensation produced by injury, inflammation or other tissue pathology. Pain is a story of a complex and highly organized central nervous system which can take nerve impulses and turn it into what we can feel as pain. More specifically pain is considered a multidimensional experience which is produced by characteristic "neurosignature" patterns of nerve impulses in a widely distributed neural network in the brain (Melzack, 2001, p. 1378). These areas include the thalamus, the somatosensory cortex, the reticular formation, the limbic system and the posterior parietal cortex (Flor, 2002, p. 184).

According to Melzack the neuromatrix takes different inputs and can produce various outputs. The inputs can be classified as cognitive-evaluative, sensory-discriminative, and motivational-affective. *Cognitive-evaluative* encompasses the tonic input from the brain, such as cultural learning, past experiences and personality variable, as well as phasic input from the brain, such as attention, expectation, anxiety and depression (Melzack, 2001, p. 1382). *Sensory-discriminative* can be trigger points on the skin, deformities as well as visual, auditive and other sensory input (ibid.). *Motivational-affective* encompasses hypothalamic-pituatery-adrenal system, sympathetic system, immune system, limbic system etc. All these inputs can vary widely between indi-

viduals since aspects such as previous experiences can influence how a current stimulus is perceived. In this neurosignature the inputs are integrated and can produce various outputs categorized as pain perception, action programs and stress-regulation programs. *Pain perception* is as the term explains the perception of pain cognitively, sensorily and affective (including feelings of stress). *Action programs* can be involuntary actions, voluntary actions, social communication and coping strategies. *Stress-regulation programs* are automatic and encompass regulations of cortisol, norepinephrin, immune system activity etc. See **figure 5.2a** for a summary**.**

Figure 5.2a (Figure 1 in Melzack, 2001, p. 1382):
An overview of the neuromatrix.



The neuromatrix distinguishes itself from the traditional view of pain, in that it does not see the experience of pain as originating from stimulus input. In contrast, stimuli merely function as mechanisms which can trigger or mold the neurosignature. The neurosignature however, takes form and originates in the neuromatrix (Melzack, 2001, p. 1380). This implicates that despite of noxious sensory input, pain is not necessarily felt. On the other hand it also implicates that pain can be experienced in the absence of stimuli. This is exactly what is observed in several cases of chronic pain and phantom pain. The relationship between stimulus and experience of pain is in this view not a cause-and-effect but a more complex phenomenon in which pain is modulated by stimulus, but can nevertheless be expressed through the neuromatrix in

the absence of stimulus. This view is more compatible with the results found in the literature investigating pain.

According to Melzack the neurosignature for the experience of pain is determined by the synaptic architecture of the neuromatrix, which is produced by genetic and sensory influences (Melzack, 2001, p. 1381). In this sense, genetics might predispose some toward the development of chronic pain and phantom pain.

This view of pain can help explain that pain can occur with only minimal input, and that pain can be absent despite of substantial noxious input. In other words, it also gives an understanding of how top-down processes can be powerful in regulating the sensation of pain. Phantom pain is also encompassed by this theory. An amputation would cause a change to the input (both the lacking of normal input as well as abnormal firing from neuromas) leading to an altered neurosignature, which might also lead to the sensation of a phantom limb (Flor, 2002, p. 184). It also explain how genetics, pain memories, pain catastrophizing and emotional states such as depression**,** all have an impact on phantom pain and why pain can occur even in the absence of painful input. It can be speculated that if pain happens to be altered, other factors like pain catastrophizing or emotional states such as depression can be altered as well. Additionally it can also explain why phantom pain is described differently among amputees (Jensen et al., 1985), due to individual neurosignatures.

A limitation to the theory however, is that even though it offers a more complex account of pain and how many variables influences the experience of pain, the theory is highly unspecific. It does not offer an account of how this happens, so the neuromatrix itself becomes a kind of a “mystery box” in which we believe the experience of pain to occur but have no idea in which proportions the different variables interact. For this reason, the theory is also difficult to test empirically.

If the results of Ramachandran & Rogers-Ramachandran (1996) were to be accounted for in a predictive coding perspective, it would likely be argued that visual feedback creates an illusion which reduces uncertainty. Based on the account of De Ridder et al. (2012), a reduction of uncertainty should in the case of phantom pain render the filling in of a phantom unnecessary, but in the case of Ramachandran & Rogers-Ramachandran only clenching spasm were relieved (1996). This might however be an expression of the degree to which uncertainty was minimized. In MacIver et al.

(2008) predictive coding could explain why phantom pain is alleviated through mental imagery. The high degree of attention being put into the phantom leg, by training and moving the limb minimizes uncertainty. This might explain the alleviation of pain which was observed in MacIver et al. (2008). Neuromatrix theory would most likely ascribe the reduction of pain due to alterations in the neurosignature, due to alternate input to the neuromatrix. In Ramachandran & Rogers-Ramachandran's (1996) case, the mirror could provide sufficient visual feedback for the brain to experience control of the limb. In MacIver et al. (2008) mental training of the phantom limb might have helped in a similar fashion by providing alternate input. The theories seem to agree that top-down processes play an important role in relation to phantom pain.

5.3 Neuroplasticity

Neuroplasticity refers to the brain being able to change through experiences and the environment (Breedlove & Watson, 2013, p. 8). By change, it is meant literally that the brain physically alters its structure depending on the input. This change is an absolute necessity for learning to occur. These changes can happen both pre- and postsynaptic, in for instance greater release of neurotransmitter or an increase in numbers or sensitivity of receptors - also called long-term potentiation. These changes manifests throughout the network in which the neuron is embedded (ibid. p. 542). As Donald Hebb (1949) explained: "*cells that fire together, wire together"* (Breedlove & Watson, 2013, p. 547). A synapse is strengthened when it successfully drives the postsynaptic cell. This is called a *Hebbian synapse* (ibid., p. 210).

Following amputation the input to the brain is changed and a series of changes occurs in the brain (Makin et al., 2015). Merzenich & Jenkins (1993) illustrated how the cortical maps can change with experience in monkeys. Several weeks after surgical removal of the third digit of the hand, most or everything of the cortical area representing the digit had been occupied by the representation of the second and third digits as well as the representation of the palm (Merzenich & Jenkins, 1993, p. 92). Merzenich & Jenkins hypothesize that since the telescoping phenomenon which has been reported, parallel the plastic changes in the cortical maps, telescoping might be

due to those changes (Merzenich & Jenkins, 1993, p. 92). Even though it could be tempting to make the connection, it should be noted that the cortical reorganization can occur in the absence of telescoping (Montoya et al., 1997). There however seem to be a relation between the two phenomena.

Cortical reorganization can also be observed in humans following amputation. As described in **section 3,** there seem to be a strong correlation between cortical reorganization and phantom pain. If neuroplasticity is a mechanism which can ultimately lead to phantom pain through cortical reorganization, this reorganization might also reversed. As already mentioned in **section 4**, this was hypothesized by MacIver et al. (2008). Giving an individual the experience of moving the phantom limb might provide sufficient stimulation that a reduction of cortical reorganization can occur.

It was once believed that the adult brain was only minimally plastic, but studies as already mentioned have changed that conviction. Makin et al. (2015) have called amputation one of the most striking demonstrations of plasticity in the adult human brain (p. 217). In their study they illustrated that cortical reorganization following amputation is not restricted to the sensorimotor homunculus. Reorganization occurs at a network-level scale of functional connectivity. Connections between the missing hand cortex and the default mode network - a network normally not active while an individual is engaged with the environment - has been found (ibid., pp. 218, 222). Based on the results of Makin et al. (2015), it could be speculated that complex experiences such as phantom phenomena can occur, due to the fact that a cascade of cortical reorganization can be elicited by local deprivation of signals following amputation.

Ramachandran and Altschuler (2009) listed several hypotheses regarding phantom pain, three of which involve neuroplasticity: 1) Central remapping can lead to the possibility of low threshold touch input to cross-activate high threshold pain neurons; 2) Remapping itself can lead to an output which might be interpreted as pain in higher brain centers; 3) Preamputation pain tend to persist as memory in the phantom (Ramachandran & Altschuler 2009, p. 1696). In order for the first of Ramachandran and Altschuler's hypotheses to be plausible, it would require that cortical reorganization extends beyond the somatosensory cortex, due to the fact that pain involves brain areas such as the anterior cingulate cortex (Wager et al., 2004) which is not

normally involved in sensations of touch. This is however also known to be the case. As already mentioned, Makin et al. (2015) reported that reorganization following amputation is far from restricted to the somatosensory cortex but includes several other areas as well, rendering the first of Ramachandran and Altschuler's hypotheses plausible. In order to test such a hypothesis, brain activity could for instance be measured during stimulation of areas closely represented to the absent limb. If nonpainful stimulation of the closely represented area can elicit expression of pain and activation of the anterior cingulate cortex it could be an indication of cross-activation eliciting the painful response.

The second hypothesis, that remapping itself can lead to an output which might be interpreted as pain in higher brain centers is on the other hand very difficult to test empirically. A series of studies establishing empirical evidence for the relation between phantom pain and cortical reorganization is needed for such a hypothesis to be tested. Of course, it is impossible to derive causality from correlations, but a series of studies might lead to stronger indications towards whether remapping itself can lead to an output being interpreted as painful.

The third hypothesis that preamputation pain tend to persist as memories in the phantom, is already a known fact (Nikolajsen, 2012; Flor, 2002). Memories of pain are however not needed for phantom pain to occur, due to the fact of reports of phantom pain in people with congenitally absent limbs. However, it seems that preamputation pain often manifests itself in the phantom, when these have been present (ibid.).

It is emphasized that even though none of the theses can be the isolated cause of phantom pain, they nevertheless have a modulating effect on phantom pain. They might at least partially account for the phenomenon.

5.4 Reflections

As mentioned in **section 4** phantom pain, or any other experience, cannot be isolated to top-down or bottom-up processes. Top-down and bottom-up are not two distinct processes, but more to be considered components of the same process. In a predictive coding perspective, there is an ongoing interaction between an internal model (top-down) and sensory inputs (bottom-up) from where the difference is passed along to reevaluate the internal model. In cases of phantom pain most peripheral input is removed, with the exception of stump neuroma which may occur. So, even though phantom pain involves both peripheral and central mechanisms, it seems that central mechanisms and the top-down component play a larger role. This notion is also supported by the neuromatrix theory of pain, which states that painful sensations arises in the neuromatrix itself and noxious information only serves to trigger or modulate the neurosignature. This implicates that pain such as phantom pain can occur even in the absence of peripheral input. This is known to be the case in chronic and phantom pain. Additionally, neuroplasticity has been a topic for the current section. Neuroplasticity is an important ability for learning to occur, however it might however have the capability of becoming maladaptive in case of for instance amputation. Taking the high correlation between phantom pain and cortical reorganization into account, the role of neuroplasticity might provide an explanation for the high prevalence of phantom pain in amputees.

Based on the understanding of the mechanisms behind phantom pain a variety of treatments can be suggested. Knowing that phantom pain does not need peripheral mechanisms to occur, treatment targeting these might not be useful. For instance, treatments such as surgical removal of neuromas would potentially only serve to ease pain temporarily, as surgical removal would cause a new insult to the nerves, potentially resulting in the creation of another neuroma. Also, surgical manipulation of the stump is not recommended (Kulkarni & Grady, 2010). Since most conventional approaches range from ineffective to only slightly effective, and with the evidence that top-down processes seem to play an essential part of phantom pain, it could be beneficial to target the top-down processes to modulate phantom pain. The current project argues that it is worth to further investigate the effects top-down processes might have in the treatment of phantom pain. This could be treating the ability to divert

attention from the pain. In a neuromatrix perspective attention can be an important factor, which can potentially eliminate pain. This has already been seen conducted in the studies of (Rosen et al. 2008; Hilgard 1967; Hilgard 1971). Another suggestion for treatment could be training the phantom limb through mental imagery to elicit activation in the deafferented brain area representing the missing limb, to reduce cortical reorganization as suggested by MacIver et al. (2008). MacIver et al. (2008) found training of the phantom limb through mental imagery to be seemingly effective in the treatment of phantom pain, and would also reduce cortical reorganization. The current project will however go in a slightly different direction, though inspired by MacIver et al. (2008). One of the main changes is to use hypnosis instead of mental imagery to enhance the vividness of the training. This is due to the promising indications of hypnosis being a powerful tool in top-down regulation of for instance pain. Sensory and motor training of the phantom in hypnosis can be considered largely a top-down regulation due to the fact it is an intervention which is internally generated by higher order brain functions. In the following section a study investigating the effects of sensory and motor training in hypnosis on phantom pain will be designed. During this description, hypnosis will be accounted for in more detail as well as the process of a hypnotic session.

6. Design

In this section the hypothesis that sensory and motor training of a phantom limb through hypnosis leads to reductions phantom pain will be operationalized. Based on the evidence accounted for throughout the project, it has been hypothesized that training of a phantom limb through hypnosis leads to reductions in:

1. Pain intensity. (MacIver et al., 2008)
2. Pain unpleasantness. (MacIver et al., 2008)
3. Pain frequency. (Based on interaction with Chief Physician Lone Nikolajsen)
4. Emotional distress, such as thought content that reflects worry, fear and inability to divert attention away from the experienced pain. (Sullivan, 2009; Vase et al, 2011)
5. Depression. (Based on interaction with Chief Physician Lone Nikolajsen).

The section will start by determining the scientific perspective and how the data should be acquired based on the aim of investigating the efficiency of this treatment. The measurements pain intensity, pain unpleasantness, pain frequency, emotional distress, and depression will be operationalized. Furthermore, intervention and control groups will be designed. The aim is to establish a valid design which qualifies to answer the hypotheses. Throughout this section each choice in the design will be discussed.

6.1 The scientific perspective

Depending on the aim of the study, qualitative and quantitative approaches have forces and drawbacks (Coolican, 2013, p. 52). Since the aim of the current study is to investigate whether training of a phantom limb through hypnosis can lead to reduction in phantom pain an experimental design would seem to be in favor. If a qualitative approach is taken, it could potentially help illuminate the personal experience and character of pain relief following an intervention, as well as how it has impacted the participant's life. Relatives could also be interviewed to uncover how they experience the patient has benefitted from the therapy. These are interesting questions,

but taking the aim of the current study into consideration - not the most relevant. What is sought is to investigate the research question in a manner which can make an assertion of the magnitude of pain reduction following therapy possible. Furthermore, the study seeks to investigate the use of the treatment as a rehabilitation method, why the results should be generalizable to the population at large. Thus, a qualitative method is hardly the optimal choice for the current design. Qualitative aspects are however far from useless, and might even be partially integrated. This point will be discussed later.

Due to the fact that quantitative methods produce data presented in discrete numbers, it also allows a larger sample and can help minimize sampling bias (Coolican, 2013, p. 47). Data can be systematized and compared with relative ease and can thus support a larger sample with limited resources. To determine an effect of the therapy in the current study, measuring variables and making the results as unambiguous as possible by analyzing them statistically is crucial. This is why a quantitative approach is the most optimal choice. It is however argued that the current study can benefit from a qualitative augmentation, in which factors such as pain reduction, pain unpleasantness, etc. can be elaborated through a brief interview with the participant.

As already mentioned in the beginning of the current section, the experimental method is the favorable method of choice due to that fact that the current study seeks to determine whether the intervention has an effect on phantom pain.

6.2 Operationalizing sensory and motor training

In MacIver et al. (2008), as already accounted for in **section 4**, mental imagery was used as the means to sensory and motor training. A main issue is however MacIver et al. (2008) is rather vague in the description of what exactly their treatment consisted of. Therefore a script will be specifically created for the current study. This script will be returned to later in this section. Another distinction between the current and the study of MacIver et al (2008) is the addition of hypnosis, which will be accounted for.

According to Kihlstrom (2012), hypnosis is a process in which a person, a *hypnotist*, gives suggestions to another person, a *subject*, with the aim of creating imagined experiences, which involves changes in perception, memory and/or actions (Kihlstrom, 2012, p. 21). A common misconception is that the subject is passively receiving suggestions during hypnosis. Quite contrary the subject is working hard to accomplish what he or she has been suggested to do (Hilgard, 1971, p. 476). As already mentioned, suggestions during hypnosis is quite distinct from those during mental imagery. A successfully suggested touch during hypnosis will be attributed to the external world (perceived as being real), whereas an imagined touch will be attributed to the imagination itself (Barnier et al., 2012, p. 156). Therefore hypnotic experiences have the potential of being more vivid than experiences during mental imagery.

The use of hypnosis leads to the question of whether it renders the therapy only applicable to a few highly hypnotizable subjects. According to Nash (2012) it is not a necessity to be highly hypnotizable to benefit from hypnosis (p. 487). It is sufficient being at least minimally hypnotizable, which accounts for 80-90% of the population (ibid.). Despite hypnotizability have long been considered a trait, several studies has illustrated that hypnotizability is to a higher extent a skill which can be trained. 50% of low hypnotizables can be trained to become high hypnotizable by simply gaining experience with hypnosis or being guided in the use of imagery strategies (Gfeller et al, 1987; Gorassini & Spanos, 1986; Spanos et al, 1986). This way, several participants will not be excluded from the current design due to the use of hypnosis compared to mental imagery.

Studies in hypnosis as treatment for pain and phantom pain have often revolved around the idea of altering the perception of the pain or by diverting attention (Hilgard, 1967; Hilgard, 1971; Montgomery et al., 2000; Oakley et al., 2002; Rosen et al., 2008). An example of an attempt to alter the perception of pain can be seen in Oakley et al. (2002), which describes a case of a patient who had an amputation of her right leg above the knee. She ranked a chiseling pain in her ankle as the worst of her pains. In the hypnotic treatment she was to image Michelangelo hammering on a block of marble with a chisel. Likewise, she was suggested to imagine a man with a chisel hammering at her ankle, and as he had finished his work, it was time for him to go on holiday (Oakley et al., 2002, p. 370). The idea was to attach the visualiza-

tion of the stone mason to the cause of her pain, and as the stone mason went away so would the pain. Despite difficulties for the patient to imagine the scenario, she was successfully alleviated from the pain, however other types of pain, such as slicing and cutting, remained unaffected by the treatment. An example of using hypnosis to divert attention from pain can be seen in Rosen et al. (2008), where the therapy consisted of relaxation, imagining a nice place and visual images associated with positive feelings (p. 45). The two participants were in other words to dissociate from the pain. After the first intervention, the alleviation of pain only lasted one day, however after a long period of intervention - more precisely 6 months and 2.5 years of monthly therapy) the pain intensity was reduced from 80 to 50 on a visual analogue scale (VAS), and frequency of pain attack was reduced by 55% (Rosen et al., 2008, p. 50).

A very unfortunate common denominator between the use of mental imagery (MacIver et al., 2008) and hypnosis as just described is the lack of transparency. What exactly was said to the participants is unknown due to the fact that the scripts have never been published, and are at most only briefly and insufficiently described. It might be hard to replicate findings using hypnosis, but not releasing the scripts renders it impossible, why the current project describe the main points of the scripts as well as releasing the full scripts for replication to be possible. An issue that should be noted is that like psychotherapy, the content of hypnotherapy is normally tailored to the individual. Like a psychologist, the hypnotist interviews his or her client to get an impression of which treatment would be the most beneficial. This poses a major problem from a scientific point of view, since it makes replication almost impossible. To address this issue in the current project, scripts will be made after the hypnotist has had the chance to meet the patients and have gotten an impression of how these scripts should be formulated. The scripts will be general and can be applied to several patients if they are adapted at a few points as indicated in the scripts. To show full transparency the scripts is published with the publication of this study.

Generally the first step in a hypnosis session is a brief interview which aim is to foster positive attitudes by demystifying hypnosis (Laurence et al., 2012, p. 234; Nash, 2012, p. 488). Mass media and much literature are saturated with misinformation about hypnosis, which is why it is a necessity to demystify it (Laurence et al., 2012, p. 234). Some of the misconceptions common about hypnosis are: The hypnotist can

make the patient do things that he or she will not remember; In hypnosis people can be made to do immoral things they would not do otherwise; Hypnosis means losing control of your behavior; The therapist will hypnotize the patient, and when the hypnosis is over, his or her problem is solved (Nash, 2012, p. 489). Suggestions will only be taken if the subject is willing to do so. The participants in the current study will be informed about these misconceptions as well as the following point: The patient will not lose consciousness when hypnotized, but all responses are fully under their control; Hypnosis is not sleeping, despite they might find themselves in a somewhat dreamy state, where they become absorbed and focused on interesting events with greater ease; They should not be trying to force the hypnotic experience to happen. They should simply let them happen if they do; Hypnosis is not something that the hypnotist does to the patient. It is only achieved in collaboration; People differ in the way they respond to hypnosis, and no one experience everything (ibid., pp. 488-489).

Next, the hypnosis itself begins. The first step is called an induction (ibid., p. 489) in which the participant or subject, is guided through a series of imaginable experiences (e.g. "*drowsiness beginning to emerge from the top of the head all the way through the body"*), with the intention of reaching a relaxed state. Afterwards a deepener is conducted, where further suggestions are made to create a stronger hypnotic experience (ibid., p. 494) (e.g. "*imaging a stair with 10 steps, each stepping making the hypnosis deeper"*). Hypnotic experiences are the successful responses to suggestions, where the individual experiences the suggested event or states (Barnier & Nash, 2012, p. 6). The therapeutic suggestions are then given (Nash, 2012, p. 497), which includes suggestions of sensory (e.g. *"Let a softness expand through all the muscles down towards the feet")* and motor experience (e.g. "*Moving both ankles back and forth").* The hypnosis will then be terminated (ibid., p. 499). The intervention will be conducted four times over the course of four week. MacIver et al. (2008) used six intervention over the course of 6-12 weeks. This might however cause some unwanted effects, due to the fact that patients who have a less intense training (six interventions over twelve week) might not benefit as much from the therapy as patients training at higher intensities. This might potentially be a confounder which will be controlled for in the current project. So the current study seeks a more rigid intervention period to eliminate intensity of the therapy as a confounder.

6.3 Sample

A sample needs to be representative if a generalization is to take place. Ideal as this is, having a truly representative sample is impossible to fulfill in practice (Coolican, 2013, p. 41). Therefore and *equal probability selection method* is used, where every case in the target population has an equal probability of being selected.

The participants will be recruited from the neurological pain clinic, AUH (Aarhus University Hospital), from the orthopaedic division, AUH, from earlier scientific studies, through recruitment notices posted in patient unions[2] and on the Facebook group "Active Amputees in Denmark" (*Aktive Amputerede i Danmark)* (see **appendix 1**). Interested recruits will contact the researcher through mail or phone, and will receive a mail with information regarding the study. If they wish to further participate in the project, they will be asked to sign a statement of consent (see **appendix 2**), and a screening will be conducted to determine whether they fulfill the criteria of participation.

As the current study seeks to investigate phantom pain, the presence of phantom pain is naturally a necessity. This will be measured by a numerical rating scale (NRS) from 0-10, where 0 is no pain and 10 is worst pain imaginable. To avoid a floor-effect and be able to detect a potential reduction, the NRS must be ≥ 3. The phantom pain should also be chronic and not an acute reaction to amputation. As mentioned earlier in **section 1** phantom pain which is of an acute character disappears or reduces by itself (Nikolajsen, 2012). Therefore it is required for participation in the current study, that the amputation occurred at least six months prior to enrollment to avoid misinterpreting a natural reduction of pain as an effect of the intervention - in other words, making a type I error (finding an effect where there is none) (Coolican, 2013, p. 349).

To make sure patients are of age participants should be between 18-70 years old. Due to the contradictory results found in the literature regarding phantom pain in people with congenitally absent limbs, these people are excluded from the current study. The existence of phantom pain in people with congenitally absent limbs have been

[2] Dansk Handicap Forbund, Diabetes Foreningen, Kræftens Bekæmpelse, og Landsforeningen af Polio-, Trafik-, og Ulykkesskadede.

reported by for instance Brugger et al. (2000) and Saadah & Melzack (1994), however Flor et al. (1998) and Montoya et al. (1998) found no cases of this. It is however not the question of the prevalence of phantom pain in people with congenitally absent limbs which pose a problem for the current study, but it is the question of whether the nature of the pain is the same as phantom pain following amputations. Furthermore, the intervention as described in the section above, assumes that the patient have had earlier experiences with actual sensation of touch and movement of a present limb.

Another factor which might have an influence on the current study is stump pain. Stump pain can be both present and absent with phantom pain. Where stump pain seems to primarily be of a peripheral character, phantom pain seems to be primarily central. Phantom pain is nevertheless influenced by stump pain (Nikolajsen, 2012, p. 3). Also, pain which is so closely placed to the phantom limb might interfere with the evaluation of phantom pain as well as exacerbating it. Since the treatment in the current study is not hypothesized to have any beneficial effects on stump pain, participants who rate their stump pain as $\geq$ 3 on a NRS (0-10) are excluded.

Another exclusion criterion is severe psychiatric disorders. Severe psychiatric disorders such as schizophrenia might potentially interfere with the hypnosis (Oakley, 2012, pp. 371-372).

The inclusion and exclusion criteria are summarized in table **6.3a**

Table 6.3a. *Inclusion and exclusion criteria for the sample in the current study*.

Inclusion criteria	Exclusion criteria
● Between 18-70 years of age. ● Amputation of upper or lower extremity. ● Minimum six months since amputation. ● Phantom pain $\geq$ 3 on NRS, 0-10	● Congenitally absent limbs. ● Severe psychiatric disorders. ● Stump pain $\geq$ 3 on NRS, 0-10

The screening has been conducted in the form of a questionnaire which determines whether the participant fulfill the criteria. See **appendix 3**.

6.4 Effect measures

To determine whether the intervention has had an effect, effect measures need to be made. In order to determine a baseline these measures will be made before the intervention (pre-test) and afterwards (post-test). Before this pre-test-post-test design is described, the effect measures which the tests will consist of will be described. From **section 3** it can be derived that several characteristics can be measured when talking about phantom pain. One obvious measure is the measure of pain intensity. This measure is however far from sufficient by itself as it captures only one aspect of the pain. In addition, MacIver et al. (2008) measured pain unpleasantness to capture an emotional component of phantom pain, which will also be done in the current study. As Ramachandran & Altschuler (2009) points out, phantom pain might be characterized by other types of emotional distress such as pain catastrophizing and depression (p. 1694). These aspects will be operationalized in the current section as well. Additionally, pain frequency will also be assessed. Since not all implications can be accounted for prior to the therapy a small interview in which the participant has the opportunity of explaining other aspects which has changed, will be conducted.

6.4.1 Operationalization of pain intensity and unpleasantness

Due to the fact that pain is a subjective and private experience the measurement will unavoidably rely on the participant's introspective abilities (Breivik et al., 2008, p. 17). MacIver et al. (2008) used the numeric rating scale (NRS), which has also been chosen for the current project. Pain intensity will be assessed with an NRS ranging from 0 (no pain) to 10 (worst pain imaginable) whereas pain unpleasantness will be assessed with an NRS ranging from 0 (no unpleasantness) to 10 (extreme unpleasantness). For future references these measures will be abbreviated to NRS_{PI} and NRS_{PU} respectively. MacIver et al. (2008) used the same operationalization of these two variables. To determine the immediate effect of the therapy, these two measures will in addition to be taken in the pre- and posttest also be taken before and after each session. To determine the effects of therapy on a day to day basis during the inter-

vention period, to acquire a more general measure less influenced by the immediate effect of the intervention, these measures will also be taken in the form of a diary the three consecutive days following each session.

Pain frequency will be assessed through three effect-measures: how many days the participant on average has pain attacks per week (PF_{days}); average number of pain attacks there have been during PF_{days} ($PF_{attacks}$); the duration of each attack in seconds ($PF_{duration}$).

6.4.2 Operationalization of emotional distress

In MacIver et al. (2008) it was argued: "*While it is difficult to describe the emotional content accurately, they* [the patients] *are able to estimate the degree of unpleasantness.*" (p. 2181, brackets added.). The current project includes pain unpleasantness as a variable. It is however not seen as sufficient to solely have unpleasantness as a measure of emotional content. In the attempt to cover emotional content of phantom pain better, the *Pain Catastrophizing Scale* (PCS) Danish version has been used.

The PCS was developed by Sullivan et al. (1995) in an effort to develop a comprehensive evaluation instrument, which involved different dimensions discussed be previous investigators (Sullivan, 2009, pp. 3-4). The PCS contains three dimensions: rumination, magnification, and helplessness. *Rumination* in the PCS refers to thinking about how much the pain hurts; *Magnification*, refers to worrying that something worse might happen; *Helplessness*, refers to thinking that the pain is overwhelming and there is nothing that can be done to reduce the pain (ibid., pp. 4-5).

The PCS consist of 13 items shared among the three dimensions. The participant is to reflect on past painful experiences, and evaluate to which degree they experience each of the 13 thoughts or feelings when experiencing pain. The participant can rate each question on a scale from 0 (not at all) to 4 (all the time) (ibid., p. 5). The PCS outputs a total score and one score for each dimension. The total score is the sum of all responses. Rumination is the sum of items 8-11; magnification is the sum of items 6, 7 and 13; helplessness is the sum of items 1-5 and 12.

In addition to PCS, depression will also be assessed to cover the emotional aspects of phantom pain. Depression will be operationalized with the Beck Depression Inventory, 2nd edition (BDI-II). The BDI was developed by Beck et al. in 1961, but came in a revised edition in 1996, after several changes to the definition of depression (Beck et al., 2005, pp. 8-10). The BDI-II is based on the criteria for depression in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) (ibid., pp. 7, 12). BDI-II is however not a diagnostic tool, but is solely used to determine the degree of depression.

The test consists of 21 items. These items can be rated on a four point scale (0-3). BDI-II outputs one single core which is simply the total sum (ibid., p. 16). The degree of depression is considered to be minimal when scoring 0-13 points, mild 14-19, moderate 20-28, and severe 29-63. As can be seen, the lowest possible score in BDI-II is considered to have minimal depression. This is again due to the fact, that this is not a diagnostic tool. It is simply a tool to evaluate the degree of depression

6.5 Pre-test-post-test

As already unveiled, the current design will be a pre-test-post-test design. The pre-test will contain a questionnaire which serves two purposes: determining whether the participant fulfill the criteria for participation and making the baseline. NRS_{PI}, NRS_{PU}, PF_{days}, $PF_{attacks}$, and $PF_{duraiton}$ will be measured (see **appendix 3**). Additionally, the pretest will contain PCS and BDI-II. The posttest will be identical to the pre-test with a little variation. It will contain the same measures but without screening. A modified questionnaire has therefore been made for this occasion (see **appendix 4**).

Figure 6.5a illustrated the design as it has been presented so far. The figure will be continuously developed throughout this section.

Figure 6.5a. *The design has taken form as an experimental pre-test-post-test design. The pretest determines the baseline for the dependent variables, which is followed by the intervention, and finished with another measurement to determine changes in the dependent variables.*

An issue however remains: How would we be able to tell that the change is in fact due to the intervention, and not other factors? This question will be dealt with in the following section.

6.6 Isolation of the independent variable

An unfortunate tendency in studies investigating the use of hypnosis in the treatment of not only phantom pain, but also pain in general is that there is only one group consisting of individuals selected for their high hypnotizability or two groups where high and low hypnotizable have been separated (e.g. Derbyshire et al., 2004; Hilgard, 1967, 1971). In essence this makes them group difference studies, which makes the groups unequal (Coolican, 2013, p. 113). Using this method is not optimal if it is the aim of the study to determine an effect of the therapy. In that case, the only thing that could be concluded in case of a significant difference from pre- to post-test, is whether higher hypnotizables show a larger difference in expressions of phantom pain following treatment than low hypnotizables. It cannot tell anything about the intervention itself. While the studies remain uncontrolled, it is not known whether the difference is caused by a placebo effect or in fact the intervention itself. To determine the effect of the intervention, the current study will make use of the true experimental design, in which participants are randomly allocated to two groups, an intervention and a control group, which have separate interventions (Coolican, 2013, p. 113).

All participants regardless of the group they will be assigned to, have to fulfill the criteria for participation to make the two groups as identical as possible. One way to

make use of controls is to have a passive control group. This is however problematic due to the fact that passive controls do not control for placebo-effects. There is no reason for a participant to believe that their pain should be alleviated, since they have not gotten any sort of treatment. To control for placebo-effects or other confounding variables, the control is identical to the intervention (described in **section 6.2**) with the exception of therapeutic suggestions. The intervention of the control group will contain a pre-hypnosis interview, induction procedure and deepening procedure similar to the intervention group. The control group will however receive suggestions of a meditative character, where breathing exercises are central. The control intervention will in this sense be a hypnotic session where sensory and motor training of the phantom limb is replaced by relaxation not related to the pain. The hypnosis is then terminated similarly to the intervention group. The control is hypothesized not to show any or only minimally reduction of phantom pain in the measure described in **section 6.4**. To control for the possibility of training intensity as being a confounder, both groups will go through the same amount of interventions: four, one time per week. **Figure 6.6a** illustrates the design so far.

Figure 6.6a. *The study is now taking form as an experimental design, consisting of a pre-test, two groups (intervention and control) as well as a post-test.*

6.7 Assessing long-term effects

To determine whether the effects observed in the current study is not only temporary, the long term effects need to be assessed. It is quite normal that effects after an intervention period go through a slow deterioration, which might not be caught by the post-test. This is why a follow-up will be conducted. It will involve the same measures as the post-test and be conducted a month after the final intervention. As mentioned in **section 6.1** a short interview will be made, where impressions regarding control of the phantom limb will be assessed. The aim with the interview is to uncover aspects that the participants might experience, but which is not caught by using traditional quantitative methods of collecting data. These aspects might include changes in their daily lives or heightened sense of control. As accounted for in **sections 2,** pain is a very complex phenomenon which implicates that an NRS-scale can hardly be justified as a complete representation of phantom pain. Therefore the interview gives the possibility that the participants can explain their pain more freely. By making this qualitative augmentation, explanations can perhaps be provided for potential oddities in the data if those happen to be present.

See **figure 6.7a**.

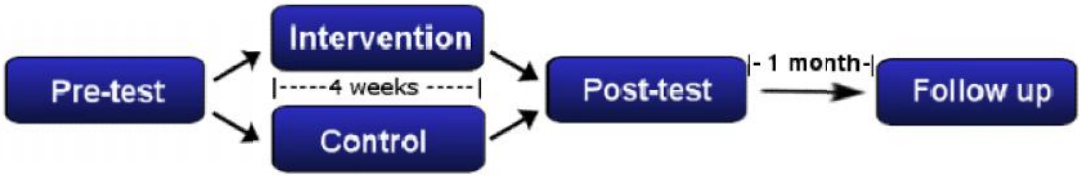


Figure 6.7a. *The full design illustrated. First the pre-test will be conducted. Then the participants are allocated to two groups. Both go through four interventions over the course of four weeks. Then the post-test is conducted. This is followed by a follow-up one month later.*

6.8 Improving validity

The design is now almost in place, however there are some different aspects which are needed to improve the overall validity. First and foremost, all procedures are standardized. Patients in both conditions are given the same information and the same instructions about the experiment. To this purpose a protocol has been created (see **appendix 7**). Questionnaires have been made and standardized tests such as PCS, BDI-II and SHSS:C are used. The latter will be accounted for shortly. The tests will be administered in the referred order.

Since this is a controlled pre-test-post-test design, it contains both repeated measures (session) and independent samples (group). Allocation is important, due to the fact that important participant variables might confound the results. Simply making a random allocation might result in unequal distribution of for instance age. If age was to be considered important in regards to the effect of the therapy, this might bias the results. In order to minimize important participant variables as being confounders the two most important have been selected as stratification parameters in order to obtain approximately the same means and standard deviations in the two groups. These two stratification parameters are hypnotizability and pain intensity. It goes without saying that hypnotizability can be an important factor in regards to the effects of therapy involving hypnosis. Pain intensity might also influence how much the participant benefits from the therapy.

Hypnotizability will be operationalized by using the Stanford Hypnotic Susceptibility Score: Form C (SHSS:C). SHSS has been used in research studying hypnosis since the 1960's (Weitzenhoffer & Hilgard, 1996, p. 1). The aim of the test was to derive a method that would permit a preliminary screening test that could determine an individual's hypnotizability. The SHSS contains 12 items with progressive difficulty. The hypnotist will evaluate whether the subject passes and item and can get 1 point per item. Scoring between 0-4 is considered low hypnotizable, between 5-7 medium, and 8 and above high (ibid.).

SHSS has often been used to select individuals who are high hypnotizable. In the present study, hypnotizability is only registered for allocation purposes. Patients who

are low hypnotizable will not be excluded from the study. This will also give a better prognosis of the therapy to amputees independent of their hypnotizability.

The enrollment of participants is expected to occur over a period of several weeks, why allocation will be done gradually. When an SHSS score is available, a match between the participant and a condition is made to make the conditions as identical as possible in terms of the stratification parameters.

The study will be a double blind in which both researcher and participant are blinded in regards to their intervention. The hypnotist will allocate to the groups and has nothing to do with testing other than SHSS:C. The researcher administering pre-, post-, and follow-up tests is unaware of the condition and so is the participant. It will be explained to participants regardless of their group, that the therapy in hypnosis can potentially reduce phantom pain. The expectancy of reduced pain is seen as a necessary mediator for hypnosis, and it is also done to constitute the control condition as a valid active control. The potential placebo effect this might result in is controlled for, due to the fact that both groups are told the same and should therefore have similar expectations.

6.9 Ethical considerations

In this final section of the design some ethical considerations will be made based on the general ethical principles of respect, competence, responsibility and integrity (Coolican, 2013, pp. 585-586). Several aspects are relevant for the current project, such as deception, debriefing, anonymity, the right to withdraw from the study as well as relevance of the measurements.

A general guideline for research is to be as open as possible regarding the aims of the study to avoid deception of the participant. In some cases however, it can be undermining for the study if the participant has some critical information. As mention earlier, the patients in the current study will be told that the therapy in hypnosis can potentially reduce phantom pain. They are however not told that they are allocated into two groups, where only the intervention group gets the treatment hypothesized to have an effect. This could be classified as being deceptive towards the participants,

but this is an absolute necessity to control for placebo. Having similar expectations is a must to maintain internal validity.

At the first treatment, the participant will be informed about anonymity as well as the right to withdraw at any time without consequences. All data is saved on a password-protected computer, no one outside the study will have access to. Identification number is given to each participant, so data sheets cannot reveal the identity of the participant. The participant will need to sign a statement of consent, which will be done to ensure that they have understood the terms of the study.

Furthermore, tests administered will be used for the sole purpose of comparison from pre- to post- and follow-up test to determine a difference. This means, that when using the PCS and BDI-II, no interpretation is made. In the light of the current study, it is completely irrelevant whether a participant is highly catastrophizing or highly depressed. It is not necessary knowledge to investigate the hypotheses.

If the intervention group has a reduction in phantom pain and the control has not, the participants in the control condition are bound to have some disappointment since they had hoped for an effect. Though it is an unfortunate situation it is the nature of an experimental design. To counter this situation, an additional study could administer the intervention therapy to the former control group. This solution has two benefits: It can give the participants a chance to receive proper treatment; and if a reduction is observed, it would provide further evidence of the effect of the therapy.

6.10 Summary

The aim of the study was to investigate the effects of training of a phantom limb through hypnosis on phantom limb pain. The section started listing the measures which were hypothesized to be reduced following therapy. These were pain intensity, pain unpleasantness, pain frequency, emotional distress and depression.

The design settled on an experimental pre-test-post-test design. See **tables 6.10a and 6.10b** for an overview of the independent and dependent variables as well as the components of each part of the design

The aim of the pretest was to determine whether the recruits fulfill the criteria of inclusion and to establish a baseline for comparison after the intervention (see **appendix 3**). The participants are then allocated into an intervention and control group. This allocation will be conducted with hypnotizability and pain intensity of the phantom pain being primary and secondary stratification parameters respectively. The therapy will consist of sensory and motor training during hypnosis whereas the therapy in the control condition will consist of hypnosis with relaxation techniques - a therapy hypothesized to have no or only minimal effect on any of the measures. The main purpose of the control group is to isolate the independent variable and to account for potential confounders. Therapies in both groups are administered four times, once per week. Pain intensity and pain unpleasantness are assessed before and immediately after each session, with the intention of acquiring a measure of the immediate effects of the therapy (see **appendix 5)**. Pain intensity and pain unpleasantness are additionally assessed the three consecutive days following therapy to acquire a more general measure, less influenced by the immediate effects of the therapy (see **appendix 6)**. Following the final session a post-test identical to the pre-test is administered. A modified post-test questionnaire is however given, due to the fact inclusion/exclusion criteria do not need to be assessed (see **appendix 4).** A month after the post-test a follow up will be made to determine the long term effects of the therapy. The follow-up test is identical to the post-test. A brief interview will be conducted in which the participant has the opportunity to tell about their experience of the therapy to capture aspects the quantitative measures have not been able to. The protocol of the study can be seen in **appendix 7**.

Table 6.10a, illustrates the independent and dependent variables in the current study. **Table 6.10b** illustrates the contents of each step of the design.

Table 6.10a. *Independent and dependent variables. NRS_{PI} and NRS_{PU} (Numerical Rating Scale for pain intensity and pain unpleasantness); PF_{days}, $PF_{attacks}$ and $PF_{duration}$ (Pain Frequency in days with attacks per week, number of attacks on days with attacks, and the duration in seconds of each attack); PCS (Pain Catastrophizing Scale); BDI-II (Beck Depression Inventory, second edition).*

Independent variables (conditions)	**Dependent variables**
- Therapy with sensory and motor training in hypnosis - Therapy with relaxation techniques in hypnosis	- NRS_{PI} - NRS_{PU} - PF_{day} - $PF_{attacks}$ - $PF_{duration}$ - PCS - BDI-II

Table 6.10b. *Content of each step in the design. See **appendices 3** and **4**. SHSS:C (Stanford Hypnotic Susceptibility Score: Form C). *The measure will be made before and after each intervention to determine immediate effects of the therapy, as well as the three consecutive days to obtain the effect more independent of the immediate effects.*

Pre-test:	**Intervention:**	**Post-test:**	**Follow up:**
- Inclusion /exclusion criteria - NRS_{PI} - NRS_{PU} - PF_{days} - $PF_{attacks}$ - $PF_{duration}$ - PCS - BDI-II - SHSS:C	- Sensory and motor training in hypnosis - *NRS_{PI} - *NRS_{PU} **Control:** - Relaxation in hypnosis - *NRS_{PI} - *NRS_{PU}	- NRS_{PI} - NRS_{PU} - PF_{days} - $PF_{attacks}$ - $PF_{duration}$ - PCS - BDI-II	- NRS_{PI} - NRS_{PU} - PF_{days} - $PF_{attacks}$ - $PF_{duration}$ - PCS - BDI-II - Interview

The methodological hypothesis can be listed as follows:

- Sensory and motor training in hypnosis leads to a reduction in
    - Numerical Rating Scale of pain intensity (NRS_{PI}).
    - Numerical Rating Scale of pain unpleasantness (NRS_{PU}).
    - Pain frequency. Days per week with attacks (PF_{days}), attacks per day with attacks ($PF_{attacks}$), and duration of each attack in seconds ($PF_{duration}$).
    - Pain catastrophizing Scale (PCS).
    - Beck's Depression Inventory, 2nd edition (BDI-II).
- Hypnosis with relaxation techniques leads to no or only minimal reduction of the measurements stated above.

6.11 Reflections

With the design in place an important question that deserves reflection is what the outcome - being significant or nonsignificant - would illustrate. Due to the fact that there a several dependent variables, it would be beyond the scope of the current project to address every single possible outcome. Therefore, only a few have been selected to illustrate what the design is capable of concluding.

First of all, it should be noted that just because a significant result is obtained does not necessarily mean that the therapy is efficient. Effect sizes needs to be taken into account as well. There is a possibility that a significant difference is found, but if the effect size is very small, the therapy might not be attractive as a potential treatment. If however the outcome illustrates a significant difference from pre- to post-test in the intervention group, a significant difference between the intervention and control, and the effect sizes seem promising, it indicates that motor and sensory training of the phantom limb during hypnosis might be an effective treatment of phantom pain. This outcome would support the findings of MacIver et al. (2008). The results might also hint at some of the potential mechanisms behind phantom pain, as the argument of top-down processes being important in regards to phantom pain is further strengthened. It might also be speculated whether sense of control is an important factor in the maintenance of phantom pain.

Another possible outcome is that significant difference is found from pre- to post-test in both groups, but not between intervention and control groups. This outcome could be produced by several factors. It could be that relaxation techniques are just as effective at reducing phantom pain as the sensory and motor training. From a clinical point of view both therapies might be useful due to the fact that they both successfully reduced pain. However, from a scientific point of view it implicates that the control was not optimal, due to the fact that it obscured the effects of the intervention group, instead controlling for confounders. The outcome could however also be an expression of a strong placebo effect. If both conditions are equally effective in reducing phantom pain it would be in contrast to MacIver et al. (2008).

Another possibility is of course a null result. A null result would not be able to tell very much regarding the effect of the therapy. The only conclusion that can be made on such an outcome is that the current project was not capable of showing an effect of the therapy. This is definitely not the same as concluding that the therapy is ineffective, due to the fact that several factors can be the cause of a null result. It could be that the therapy is ineffective in the treatment of phantom pain, but it is also a possibility, as this is an original study and therefore untested, that the power is too low. It could be that the protocol just needs minor adjustment to increase the power dramatically. If however, several studies with high power were made and still no significance was obtained, it might further support the idea that the therapy might not be efficient. However, such a conclusion would be pure speculation if it was based solely on the current design in case of such an outcome.

The author of the current project argues that when dealing with terms like hypnosis transparency is of high importance. In earlier studies hypnosis has been variously defined and often portrayed in an almost mystic way. Studies using hypnosis is often characterized by insufficient explanations of the content of their scripts. Scripts are also rarely published rendering replication close to impossible. If hypnosis is to continue gaining ground in research and not remain case-studies, it is necessary that scripts are published. This way replication is made possible and some degree of standardization can begin. Hypnosis seem to have a lot of potential but without properly designed research which is transparent in regards to its intervention, hypnosis will continue to be a term enveloped in preconceptions which might cloak an actual effect. With this degree of transparency, a pattern might start to emerge which

can help elaborate on the findings of effects of hypnosis as well as explain potential null results.

7. Pilot Study

Having established a design to investigate the hypothesis that phantom pain can be reduced through sensory and motor training during hypnosis, this section will now seek to test the paradigm. This will be conducted as a pilot study. A few changes have however been made. First of all, since this is a test of an effect at an early stage, only the intervention group has been included. Due to this fact, hypnotizability test has been omitted, since its purpose was to set a stratification parameter for the allocation. Secondly, no follow-up will be conducted due to the short time-span of the current project.

The recruitment was conducted in accordance to the method described in **section 6.3** and during a period of three months, only six participants had been acquired. Of those six, four were excluded due to reasons of excessive stump pain, amputation within the six months, or other reasons. The participants were screened and pretested with a questionnaire (see **appendix 3**), PCS and BDI-II. They then went through four interventions over the period of four weeks. Hypnotist Jeppe Schjøtz conducted the therapy, and the script used can be seen in **appendix 9.** Afterwards a post test was conducted (see **appendix 4)**. Furthermore, a small interview was conducted in order to give the participants an opportunity to express aspects not captured by the tests.

For the pilot testing two pilots were successfully recruited. To ensure the participants' anonymity, pseudonyms for the patients have been made. The first participant, who will be referred to as "John" was a 63 year old male. His amputation was conducted in 2009, due to an ischemic stroke in his right leg. After a failed surgery it led to gangrene leaving an amputation near the hip a necessity. When John entered the study he expressed how he felt phantom pain exclusively on the top of his foot, despite the fact his leg was missing from the waist. In fact he described how he had no sensation of the leg at all, even though he felt his foot being located in the shoe. In this sense, he felt his foot as not being directly attached to his body. He expressed how his phantom foot had always been impossible to move. He had been struggling with phantom pain for more than six years, when he enrolled in the current study and he told that nothing so far had helped, including mirror therapy.

The other pilot who participated in the current project will be referred to as “Peter”. He was a 50 year old male and had his amputation conducted in 2012. Like John, the amputation was due to an ischemic stroke in the leg, where the operation had not been sufficient and ultimately led to amputation of his left leg above the knee. Peter described his phantom pain as being located in his foot. His pain was severely worsened after a failed gastric bypass in which he slipped into coma twice and was revived after being clinically dead. Peter described how the pain felt like an electric charge building up in his foot leading to a sudden discharge roughly every 20th second. Pain medication could however take the worst of these pains. In addition to phantom pain, Peter described how it felt like a child was constantly pouring sand on his foot. He described this sensation as being non painful, but nevertheless a nuisance which medication had no influence on.

Neither John nor Peter suffered from stump pain. In the section to come results from the study is presented.

7.1 Results

In the current section the results will be presented. These include data from pre- and post-test, as well as the immediate results of therapy and the general rating of pain in the consecutive days following therapy. The interview, which has been mentioned in **section 6.1**, will be presented in the discussion.

Peter had to withdraw after the third intervention due to personal reasons why his overall intervention period was shortened. Unfortunately, post-test data could not be obtained from Peter, why nothing can be concluded on these measures. Pre-test data has therefore been omitted from this section, but can be seen in **appendix 9**.

The scores from John’s pre- and post-test are illustrated in **table 7.1a.**

Table 7.1a: *John. Measures of pain intensity (NRS_{PI}), pain unpleasantness (NRS_{PU}), pain frequency (PF_{day}, $PF_{attacks}$, $PF_{duration}$), pain catastrophizing scale (PCS) and Beck Depression Inventory, second version (BDI-II) for pretest and posttest.*

Dependent variable		**Pre-test**	**Post-test**
NRS_{PI}		*10*	*10*
NRS_{PU}		*10*	*10*
PF_{days}		*4*	*4*
$PF_{attacks}$		*10*	*1*
$PF_{duration}$		*120*	*60*
PCS	Rumination	*9*	*8*
	Magnification	*5*	*3*
	Helplessness	*11*	*7*
	Total	*25*	*18*
BDI-II		*19*	*18*

In **table 7.1b**, the immediate effects of each session are illustrated. NRS_{PI} and NRS_{PU} are measured before and after each session and presented for each pilot in the following table, to give an impression of the immediate effects of the therapy.

Table 7.1b: *Measures of pain intensity (NRS_{PI}) and pain unpleasantness (NRS_{PU}) immediately before and after each session. (X) Data was not available for Peter due to the fact he could not attend his final session.*

	De-pendent variable	**Session 1**		**Session 2**		**Session 3**		**Session 4**	
		Before	After	Before	After	Before	After	Before	After
John	NRS_{PI}	*1*	*0*	*2*	*0*	*1*	*1*	*1*	*1*
	NRS_{PU}	*1*	*0*	*0*	*0*	*1*	*1*	*1*	*1*
Peter	NRS_{PI}	*2*	*1*	*3*	*0*	*2*	*1*	*(X)*	*(X)*
	NRS_{PU}	*1*	*0*	*3*	*0*	*2*	*0*	*(X)*	*(X)*

In **table 7.1c**, NRS_{PI} and NRS_{PU} are presented for each pilot the three consecutive days after each session. The purpose of this measure was to give an impression of the general effects of the therapy, less influenced by the immediate effects.

Table 7.1c: *Measures of pain intensity (NRS_{PI}) and pain unpleasantness (NRS_{PU}) the three consecutive days after each intervention.*

	Session	**Day after session**	**NRS_{PI}**	**NRS_{PU}**
John	Session 1	1	*1*	*0*
		2	*1*	*1*
		3	*10*	*10*
	Session 2	1	*1*	*1*
		2	*1*	*1*
		3	*1*	*1*
	Session 3	1	*1*	*1*
		2	*1*	*1*
		3	*1*	*1*
Peter	Session 1	1	*1*	*1*
		2	*1*	*1*
		3	*0*	*0*
	Session 2	1	*1*	*1*
		2	*1*	*1*
		3	*1*	*1*
	Session 3	1	*1*	*1*
		2	*1*	*1*
		3	*1*	*1*

For John, there was no change from pre- to post-test in the measures of pain intensity, pain unpleasantness and number of days per week with pain attacks. However a large decrease in number of attacks on days with attacks was seen (from 10 to 1 attack) and the duration of each attack were halved (from 120 to 60 seconds). A decrease was also observed in pain catastrophizing scale (25 to 18) with the subscale helplessness seeing the largest decrease. BDI-II went from 19 to 18 which is virtually unchanged.

In the two first sessions pain intensity was reduced to 0 immediately after treatment. However, no reduction was seen after treatment in the two final sessions. Pain unpleasantness was also reduced to 0 immediately after the first session, and was already evaluated 0 at the beginning of second session. No reduction was seen after sessions three and four. Pain intensity and unpleasantness measured the three consecutive days following each session were unchanged.

For Peter a reduction in both pain intensity and unpleasantness occurred immediately after every session. Pain intensity and unpleasantness measured the three consecutive days following each session were unchanged.

7.2 Discussion of results

In this section the results of the pilot study will be discussed. The discussion involves an evaluation of what can and cannot be concluded on the basis of the pilot data, how these results relate to the literature, and how aspects uncovered in the interview relate to the mechanisms involved in phantom pain. Furthermore, the feasibility of the paradigm will be evaluated and suggestions for future improvements will be made.

As illustrated in the former section, John had no reduction in pain intensity (NRS_{PI}) or pain unpleasantness (NRS_{PU}) from pre- to post-test. As this study investigated sensory and motor training of the phantom limb through hypnosis, this inability to show an effect does not support the findings of MacIver et al. (2008). Of course it should noted, that as this is pilot data, there could be a variety of reasons why no effects were seen in these measures. These will be discussed later in this section.

However, if these results are representative of the actual effects of the therapy, it would oppose MacIver et al. (2008).

John neither showed a decrease in the measures of depression (BDI-II) nor in number of days per week with pain attacks. On the other hand, he showed a large decrease in the number of attacks he experienced on day with attacks (from 10 to 1), and the duration of these attacks were halved (from 120 to 60 seconds) following therapy. Whether these effects are due to the therapy can of course not be concluded at this point, as this is a pilot study in its early stage, which took its point of departure in only two participants not investigating the control condition. It is however a remarkable reduction and it is a positive indication for the feasibility of the study. In addition a reduction was seen in pain catastrophizing (PCS) mainly in the subscale helplessness.

Pain intensity was reduced to 0 immediately after the first two sessions. Pain unpleasantness was also reduced to 0 immediately after the first session, and was already evaluated 0 at the beginning of second session. It should here be noted, that pain intensity and unpleasantness were evaluated low before the onset of the therapies, due to the fact that John was on pain medication. This could potentially cause a floor-effect, in which no or only minor changes can be observed, due to the fact that low evaluation of pain was the baseline, from which only minor improvement can be expected. It could be speculated, that if pain had been evaluated higher before the session, the therapy could have shown a larger immediate effect. In MacIver et al. (2008) the patients did not take any analgesics with the exception of one who were told to abstain from the analgesics 12 hours prior to the measurement (p. 2182). A change that could be suggested to improve the paradigm of the current study would be to have the participants abstain from analgesics up to each session, to gain a measure less likely to be limited by a floor-effect. This could also be speculated to account for the lack of change seen the three consecutive days following each session. Analgesics can account for the low immediate effects as well as the low general effects, but it does not account of the lack of reduction seen from pre- to post-test.

For Peter pain intensity and unpleasantness were reduced to 0 immediately after each session. The most prominent reduction was seen in session two in which pain intensity and unpleasantness went from 3 to 0. These effects did however not seem to mani-

fest in the measures the three consecutive days after each therapy, as they remained unchanged.

In addition to the results presented in the former section, John described how he only felt pain in his foot, despite the fact his leg was missing from the waist. As mentioned in the **section 3**, this is quite often what amputees describe. Pain is more often localized in the distal compared to the proximal parts of the limb. This can be speculated to be due to the fact that the distal parts of limbs (e.g. hands and feet) have larger cortical representations (Nikolajsen, 2012). After an inflammation of the prostate, he described his phantom pain as getting worse. He also described how his phantom pains intensified during urination. This is once again, one of the descriptions people with lower limb amputations often give (ibid.). The cortical representation of the foot is closely located to the representation of the genitals. It can be speculated, as Ramachandran and Altschuler (2009) hypothesize, that the representation cross-activates neural networks normally only associated with pain. This could implicate that the expanded representation of the genitals cross-activates neural networks normally only associated with pain in the foot during urination.

At John's third treatment, he reported that he had not taken morphine in one and a half week. He had been used to take morphine 2-3 times a week for the past six years. In this context he described how he felt that the treatment worked, but simultaneously being afraid to believe too much in the effects, since most former treatments had been unsuccessful. Interestingly, he described how the pain he experienced in his foot had started to migrate. Before he was enrolled in the current study the pain was located on the top of his foot, but it had started to withdraw towards the ankle. After the fourth session the pain had moved to his shin. It should be noted that previously he had not been able to feel his leg at all. Four days after the termination of the treatment, John described how the pain in his shin had migrated back to the same spot on the top of his foot as when he had first enrolled in the study. The fact that the phantom pain started to change could indicate potential for longer lasting effects of the treatment. It would be worth investigating if migration of the painful sensation was related with changes in the cortical maps. Furthermore, John explained that had started taking morphine again. This happened shortly after he had acquired a new socket for his prosthesis, which may have had an influence.

Peter described how it felt like a child was constantly pouring sand on his foot. He described this as more of a nuisance than painful. Off pain medication, he described a painful sensation in his foot similar to an electric charge building up leading to a sudden discharge roughly every 20th second. After the failed operation of his leg which ultimately lead to amputation, Peter experienced he had been rendered incapable of moving his ankles and only just able to move his toes. This seems to strengthen the argument that phantom sensations can be influenced by memories of sensations prior to amputation. Despite describing how he immediately after treatment had no pain or unpleasantness in his leg or foot, he experienced an intense pain in the phantom calf during the first session from which he could not recover until after the hypnosis had been terminated. His pain gradually disappeared completely over the course of 10 minutes. He described how he felt like he had trained his leg intensively - like running a marathon. His pains were completely gone and replaced with a comfortable fatigue. He described the pain coming as he "descended the stairs" in the hypnosis script, and got even worse, when he was suggested to move his foot. He however described that he had a hard time pinpointing the escalation of pain to exact moments during the hypnosis. One might speculate, whether being suggested to move his foot somehow went against his preconceptions of not being able to move his foot. Furthermore, he described how he had always been prone to have pain in his calves before the amputation, which was where his pains were primarily located during the attack. It is worth speculating whether this phenomenon occurred due to a memorized pain as Flor (2002) describes, and whether the memorized pain from immediately after the amputation or the tendency to have pain in the calves, could contribute to this reaction. Interestingly the pain disappeared completely 10 minutes after the therapy had been terminated. It was evaluated that if this would happen again at the second therapy, he would be pulled from the study. After the therapy he did not feel the pain or the sensation of sand being poured on his feet for three days. The night before the second intervention he felt the pain and sensation of sand return. Despite taking his drugs as usual he was kept awake most of the night by the pain. When he came back to the second therapy his pain evaluation had been unchanged from the night before. During the second session he did not experience the elicitation of pain he had during the first session. Peter described how the pain he had evaluated completely disappeared when he was taken out of the hypnosis. His pains were completely gone as well as unpleasantness related to it. He exclaimed how he was puz-

zled by the fact that the treatment had alleviated the pain the drugs were not capable of. He reported how he could feel the pain had vanished, but he had the sensation that the pain was lurking in the background without being regarded as painful. Where he had felt exhaustion in his calf during the first treatment, he now reported a warm and pleasant sensation in his leg and foot without any kind of fatigue. He described it as if the blood flow had been restored to his phantom leg. During the talk after the treatment, he described how he slowly moved his phantom foot, despite normally having difficulties to perform this action. This time the effects only lasted 10 minutes after he had left, before the pain returned in same strength as before. Interestingly, Peter described like John, that he experienced that his phantom pain had migrated up the leg - more specifically to the calf. In addition to the pain, his phantom sensation of sand being poured onto his skin had moved along with the pain.

The small difference in the measures of pain intensity and unpleasantness before and after each session is possibly due to a floor-effect caused by the fact that the participants were on analgesia. In this sense only a very small difference in the measurements of immediate effects was detected. Despite no effects were seen from pre- to post-test in the measures of NRS_{PI}, NRS_{PU} and PF_{days}, the fact that such a substantial reduction in $PF_{attacks}$ and $PF_{duration}$ were seen, illustrates a potential use of the treatment. It should be kept in mind, that the results presented are pilot data, and thus not controlled. Whether the effects seen in the current study can be ascribed to the treatment or placebo-effects cannot be concluded until the full scale study has been conducted. The results of the current study however suggest that it is worth continuing research in the paradigm.

The fact that changes in the measures of pain intensity and unpleasantness was often seen immediately after each session but not in the three consecutive days following therapy, may be an indication that the intensity of the therapy should be increased. This could for instance be administered by having recordings of the hypnosis session the participant is to rehearse every day, with the aim of prolonging the immediate effects, hopefully, making them more general.

As mentioned in **section 7** it seems that acquiring participants to the current study can be rather difficult. This might be due to several factors, such as exclusion criteria or simply the location of the current project. The current project was limited to a fa-

cility at Aarhus University Hospital, so participants had to live nearby. Several individuals reported that they were interested but could not participate due to the location. In addition, they had to finance their own transport. These factors might contribute to the low number of participants. After a dialogue with Chief Physician Lone Nikolajsen it was made clear that this particular group can be hard to acquire, and a long period of enrollment should be expected and taken into account.

The pilot study has shown several indications that continuation of the study is feasible.

8. Conclusion

The current project set out to investigate the question:

How can the mechanisms involved in phantom pain be explained?

Phantom pain is a complex phenomenon which despite being the topic of research for many years, still little is known about it. A tremendous amount of mechanisms influences the phenomenon. These mechanisms involve both peripheral and central aspects. Among peripheral aspects, phantom pain is known to correlate with stump pain (Desmond & MacLachlan, 2010; Kooijman et al., 2000), phantom pain can be modulated or exacerbated by ectopic discharge from a neuroma (Nyström & Hagbarth, 1981), and skin temperature at the stump is known to correlate with phantom pain (Katz 1992). A sensitization of neurons located in the dorsal horns can also affect phantom pain, by making the neurons more prone to fire (Flor, 2002). Among central aspects are: Cortical reorganization correlates very strongly with phantom pain (r=0.93) (Flor et al., 1995); Phantom pain often seems to share characteristics with preamputation pain, suggesting that memories play a role as well (Flor, 2002); Regional anesthesia is only able reduce phantom pain in some instances (Birbaumer et al., 1997); Top-down processes like attention, depression or pain catastrophizing can exacerbate phantom pain (Vase et al, 2011).

Several treatments have been suggested, but so far none have shown satisfactory results from a clinical point of view. The most promising indication however seem to come from more unconventional approaches to treatment such as mirror therapy, suggested by Ramachandran & Rogers-Ramachandran (1996), or training of the phantom limb through mental imagery suggested by MacIver et al. (2008). Common for these are they seem to primarily target top-down components of phantom pain. Top-down and bottom-up are of course components of the same process, so the two terms are to be considered abstractions. Despite the two being components of the same process, it is possible that one has a larger impact on some experiences. In the case of phantom limb pain, that is argued to be the top-down component. This is partially due to the fact that no stimuli from the periphery are necessary for phantom limb pain to occur, as well as the major impact memories can have on phantom pain. Theories of for instance Flor (2002) describes phantom pain as being memories of

pain, however there are cases described, where phantom pain has been present in people with congenitally absent limbs (Brugger et al., 2000; Saadah & Melzack, 1994). Whether the nature of phantom pain in congenital amputees is identical to the nature of the pain in traumatic amputees is unknown. Nevertheless, memories can affect the character of the pain. Predictive coding also ascribes a central role to the top-down component, though it is still in dialogue with the bottom-up component. Predictive coding can help give an understanding of how the top-down component is capable of overruling signals provided by signals from the periphery. In this sense, it explains how the brain would be able to provide sensation of a phantom as a way to "fill in" the missing information from the periphery, but why this sensation can be painful and the mechanisms of how it actually emerges still seems to be an unsolved question. The neuromatrix theory of pain helps providing a structured description of how different components from the peripheral and central nervous system together constitute and modify sensations of phantom pain. It also assigns a modulating effect of signals from the periphery and does not portray the signals as the carriers of painful sensations. In the neuromatrix theory pain arises inside the neuromatrix, so signals provided in a bottom-up fashion only acts as a component in the constitution of pain. In this sense, painful experiences might not arise despite of nociceptive information. On the other hand, it also implicates that painful experiences can arise without nociceptive information, like in the case of phantom pain. The issue with the neuromatrix theory is however it does not account for the proportions in which different component can contribute to the sensation of pain, and why phantom pain arises.

Having established the top-down component as carrying a special importance in regards to phantom pain the treatment was suggested to attempt to tap into this aspect. Training of the phantom limb through hypnosis was suggested. The study was designed with the aim of establishing an investigation of top-down regulation of phantom pain. Former studies such as Ramachandran & Roger-Ramachandran (1996) and MacIver et al. (2008) could not conclude that the effects observed were in fact due to the therapy, due to the fact that the studies lacked control. This is a general tendency in these unconventional approaches along with several studies in hypnosis. Therefore the design was made as an experimental study in which both intervention and control groups were included.

Pilot data was then acquired which illuminated some potential issues in the design which needed to be addressed. In the case of John a substantial reduction in pain frequency in the measures of number of attacks on days with attacks, and the duration of each attack was found. Attacks went from 10 to just 1 attack on days with attacks, and the duration of each attack was halved from 120 seconds to 60. A decrease in pain catastrophizing scale was found (from 25 to 18) with the largest decrease in the subscale of helplessness. No effects were found in any other measures including pain intensity, unpleasantness, number of days with attacks per week, or BDI-II. The fact that no effects were found in pain intensity or unpleasantness goes against the reports of MacIver et al. (2008). A small immediate effect was also observed in pain intensity and unpleasantness the two first sessions but not during the two final. A small immediate effect was in the case of Peter observed in all the sessions. However, no effects were seen in the more general measures. The fact that the participants were on pain medicine, might have caused a floor effect in which no effect was seen, due to the fact that they already rated the pain as low. It was suggested that in a future version of the study, participants should not be taking analgesics prior to the treatment. Furthermore, to increase the effects on the general measure the three consecutive days following therapy, the hypnosis session could be supplemented with daily training tasks the participants can do at home. This is suggested due to the fact that a small effect is seen immediately following therapy, so supplementing with daily training tasks could potentially increase the effect.

Any conclusions regarding the effect of the therapy cannot be made, as this is a pilot study, however indication provided by the pilot data, illustrates the paradigm being feasible and can potentially be enhanced by the suggested elements. The full scale study is necessary to provide conclusions regarding the effect of the therapy itself.

9. Finalizing thoughts

A quite peculiar phenomenon was uncovered during piloting of the design. Both pilots reported that their phantom pain started to migrate over the course of therapy. Both described how the pain had started in their feet and had migrated to shin or calf, before returning after the study had ended. It is suggested, that this finding should be supplemented with brain imaging techniques, to determine whether the migration of the phantom pain is also reflected in a reorganization of the cortical maps. This would further contribute to investigating of the relation between cortical reorganization and phantom pain. This link has been a returning issue throughout the current project and also in the literature in general. In other words, is phantom pain a story of maladaptive neuroplasticity? Albeit an interesting question, it is not easily answered, due to its causal nature. Neuroscience can provide investigations of correlation between the two phenomena. However, causality cannot be derived from correlations. What is needed is a series of studies establishing empirical evidence to make stronger indications of the connection between the two phenomena. The study designed in the current project did not aim to provide evidence of cortical reorganization, however with a few modifications it could contribute to the investigation. With the addition of brain imaging techniques such as functional magnetic resonance imaging (fMRI), it could be explored whether a reduction in cortical reorganization occurs in individuals who experience pain relief following therapy. Finding such a reduction would support the study of MacIver et al. (2008) as well as Ramachandran & Altschuler's (2008) hypothesis that cortical reorganization plays a role in phantom pain. Again, it will not be possible to conclude whether the therapy is effective because it reduces cortical reorganization and thereby phantom pain or vice versa, but it would be a step further in the investigation of the relation between the two phenomena.

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