Aus dem Zentralinstitut für Seelische Gesundheit

Institut für Neuropsychologie und Klinische Psychologie

(Wissenschaftliche Direktorin: Frau Prof. Dr. Dr. h.c. Herta Flor)

Cortical representation of illusory body perception in healthy persons and amputees: implications for the understanding and treatment of phantom limb pain

Inauguraldissertation

zur Erlangung des Doctor scientiarum humanarum (Dr. sc. hum.)

an der Medizinischen Fakultät Mannheim

der Ruprecht-Karls-Universität

zu

Heidelberg

vorgelegt von

Christopher Milde,

M. Sc. Biologie

aus

Emden (Niedersachsen)

2017

Dekan: Herr Prof. Dr. Sergij Goerdt

Referentin: Frau Prof. Dr. Dr. h.c. Herta Flor

Table of contents

LIST OF ABBREVIATIONS

- fMRI = functional magnetic resonance imaging

- M1 = primary motor cortex

- SI = primary somatosensory cortex

1   INTRODUCTION

Various sensory and motor signals are continuously integrated with an internal model of the body to form mental and neural representations of the body (de Vignemont, 2010; Moseley, Gallace, & Spence, 2012). This multimodal integration process provides us with a coherent perception of the body embedded in a world (Tsakiris, 2010). Conditions of chronic pain and various neurological syndromes are characterized by alterations in these mental and neural body representations (Foell, Bekrater-Bodmann, Diers, & Flor, 2014; Rousseaux, Honoré, & Saj, 2014). Both, illusory body perception (Tsay, Allen, Proske, & Giummarra, 2015) and altered cortical representations of the affected body part (Flor et al. 1995; Karl et al. 2001; Vartiainen et al. 2008, 2009) have been reported. Chronic pain patients, for instance, have been shown to have impairments in two-point discrimination thresholds, problems to localize body sites on their affected body part or perceive their affected body part to be enlarged (Lewis et al., 2010; Maihöfner, Neundörfer, Birklein, & Handwerker, 2006; Wand et al., 2013).

Various types of multimodal body illusions employing mirrors, virtual-reality (Chan et al. 2007; Foell et al. 2014) or artificial limbs (Christ and Reiner, 2014) have been used to normalize altered body representations and to relieve pain or motor disabilities. The frequent co-occurrence of altered body perception and chronic pain and the efficacy of multimodal body illusions in the treatment of chronic pain, points towards a mechanistic link between altered body representations and chronic pain also at a neural level (Bekrater-Bodmann, Foell, & Flor, 2011; Tsay et al., 2015). A deeper understanding of the contextual factors and neural mechanisms of such multimodal body illusions is thus promising for the development of novel therapeutic interventions and a better understanding of the psychobiological underpinnings of various chronic pain syndromes (Bekrater-Bodmann et al., 2011; Wand et al., 2013).

The amputation of a limb is particularly suited to study the relationship between altered body representations and chronic pain since an altered representation of the body is clearly evident in amputees, where the missing body part is often still perceived as a phantom body part (Sherman, 1997). Moreover, phantom pain is a common consequence following amputation (Kooijman, Dijkstra, Geertzen, Elzinga, & van der Schans, 2000) and an amputation is associated with loss of coherent

sensory input and altered motor behavior, both factors associated with the updating of internal body representations (Moseley & Flor, 2012; Palermo, Di Vita, Piccardi, Traballesi, & Guariglia, 2014).

The present thesis aims at contributing to our understanding of the role of experimentally manipulated body perception in chronic pain and disability conditions. Therefore, the psychobiological correlates of a novel mirror visual feedback device, visually recreating a percept of having a functional limb, as well as stimulus-driven alteration in phantom limb perception were investigated in healthy persons and unilateral upper-limb amputees. The following sections provide an overview of common definitions and concepts referring to mental and neural body representations (section 1.1.), post-amputation phantom phenomena and the use of multimodal body-illusions with a particular focus on mirror visual feedback in the treatment of phantom pain following amputation (section 1.2).

1.1 Mental and neural representations of the body

When talking about the neural representation of the body, it is important to bear in mind that there are a multitude (if not infinite number) of mental representations of the body (de Vignemont, 2010). This is not surprising considering the variety of aspects that are involved in body perception such as touch, vision, proprioception, or motor behavior including emotional and semantic concepts of the body. Therefore, more than a single neural representation of the body has been referred to (Medina & Coslett, 2010; Ruzzoli & Soto-Faraco, 2014).

One approach to define body representations is based on the neuropsychological principle of double dissociation: A double dissociation is present when a subject or a group of subjects is impaired in ability A, but not B and another subject or group of subjects is impaired in B, but not A, implying two independent processing systems for A and B. Based on this principle a dyadic and even a triadic taxonomy of body representations was proposed (Berlucchi & Aglioti, 2010; de Vignemont, 2010; Schwoebel & Coslett, 2005). The dyadic taxonomy comprises the distinction between body schema and body image (Bonnier, 1905; Head & Holmes, 1911; Paillard, 1980, 1999). The body schema is defined as the sensorimotor representation (based on afferent and efferent information) of the body that guides actions, while the body image encompasses all the other body representations that are not involved in

3

planning and performing actions including a visuospatial, topographical description of the body, but also conscious perception, beliefs and attitudes towards the body by its owner (de Vignemont, 2010). One double dissociation that has been proposed for the dyadic taxonomy rests upon the dissociation between sensorimotor deafferentation (body schema) and numbsense (body image) (Paillard, 1999). Numbsense is defined as a tactile deficit with preserved tactually guided movements, whereas sensorimotor deafferentation is characterized by loss of tactile and proprioceptive information (de Vignemont, 2010). The triadic taxonomy of body representations preserves the concept of the body schema as a sensorimotor representation of the body, whereas the vague concept of the body image is further divided into the visuo-spatial 'body-structural description', which represents a topological map mainly derived from visual input that defines body part boundaries and relationships between body parts, and the 'body semantics', which represents conceptual and linguistic descriptions of the body (e.g., functional descriptions of individual body parts) (de Vignemont, 2010; Schwoebel & Coslett, 2005). The triadic taxonomy of body representations is referring to the triple-dissociation between apraxia (disorder of motor planning), autotopagnosia (mislocalization of body parts and bodily sensations) and body-specific aphasia (loss of lexical knowledge of body parts) (Schwoebel & Coslett, 2005). So far, there is no accepted taxonomy on body representations and the terms body image and body scheme have been used sometimes with opposite meanings (Berlucchi & Aglioti, 2010).

1.1.1 Body illusions in the study of altered body representations

A means to study the mechanisms of body perception is the investigation of the consequences of ambiguous multisensory input on body perception and associated psychobiological responses (Blanke, 2012; Tsakiris, Carpenter, James, & Fotopoulou, 2010). It has been shown that there is no one-to-one mapping between the perceived and the physical body (Chen et al. 2003; Blankenburg et al. 2006). For instance, in the tactile funneling illusion, short simultaneous vibratory stimulation are applied at different but nearby locations of the skin leading to the perception of only a single pulse positioned between the stimulation sites (Hayward, 2008). This illusion is related to a percept- rather than a stimulus-related representation in SI (Chen, Friedman, & Roe, 2003). These findings indicate that the brain represents perceptual rather than physical properties of the stimulus. Indeed, perception can be in

discrepancy to the physical world especially in situations of ambiguous multisensory input (Blanke, 2012).

The rubber hand illusion originally introduced by Botvinick and Cohen (1998) is a body illusion, where synchronous stroking of a visible artificial hand and a hidden actual hand can manipulate the feeling of one's self by inducing the perception of body ownership for the artificial hand (Botvinick & Cohen, 1998). Blanke et al. (2015) distinguished between non-bodily multisensory integration, only involving the integration of exteroceptive cues (e.g., audio-visual integration), and bodily multisensory integration, also involving bodily signals (e.g., visuo-proprioceptive integration). This distinction may be important since multisensory integration with bodily signals involves the remapping of sensory-dependent reference frames to a common reference frame determined by the position of the individual body parts (Botvinick & Cohen, 1998) or the whole body (Lenggenhager, Tadi, Metzinger, & Blanke, 2007). Multisensory integration with bodily signals is not only determined by laws of space, time and inverse effectiveness, important for non-bodily multisensory integration, but also by the four constraints proposed by Blanke et al. (2015) (**Fig. 1**). For instance, subjects are faster in correctly localizing a visual target when an auditory stimulus was presented shortly before (temporal law: temporal coherence between the different stimulus modalities) at the same location (spatial law: spatial congruence between the different stimulus modalities), or the weaker the effectiveness of each modality-specific stimulus is (law of inverse effectiveness) (Stein, Stanford, & Rowland, 2014).
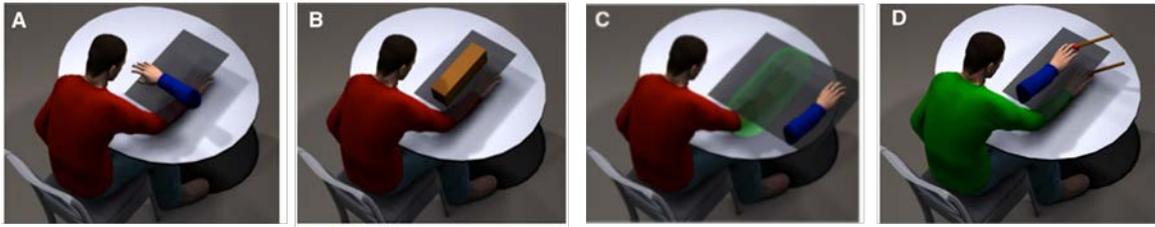
Figure 1 The four constraints on illusory ownership for a fake arm A. Proprioceptive constraint: The fake arm must be presented in a biophysically appropriate position; **B.** Body-related visual information constraint: An object will not be incorporated when it does not resemble the body; **C.** Peripersonal space constraint: The fake arm must be presented within the space surrounding the real hand; **D.** Embodiment constraint: The fake arm will not be incorporated when the fake and the real arm receive asynchronous visuo-tactile input. Figure adapted from Blanke, Slater, & Serino (2015).

According to Blanke et al. (2015), there are four constraints which have to be fulfilled to either perceive a normal body or, in case of ambiguous multimodal input, a body illusion: (1) proprioceptive constraint: for instance, the rubber hand illusion does not work when the artificial hand is placed in a biophysically implausible position (Costantini & Haggard, 2007) (**Fig. 1a**) (2) body-related visual information constraint: an artificial object is not embodied, when it has a non-bodily shape (Tsakiris et al., 2010) (**Fig. 1b**) (3) peripersonal space constraint: the artificial limb is not incorporated when it is outside of the surrounding space of the persons' limb being touched (Lloyd, 2007) (**Fig. 1c**) (4) embodiment constraint: the embodiment of the artificial hand can only occur when the artificial and actual hand receive synchronous visuo-tactile stimulation over a prolonged period of time (**Fig. 1d**).

In contrast to Blanke et al. (2015) however, research on body illusions has shown that objects that do not resemble the body can be incorporated (Maravita & Iriki, 2004). Furthermore, it has been demonstrated that body ownership can also be induced for extreme virtual limb sizes (Kilteni, Normand, Sanchez-Vives, & Slater, 2012), virtual bodies with associated proprioceptive drifts towards the avatar (Lenggenhager et al., 2007) or even a portion of empty space (Guterstam, Gentile, & Ehrsson, 2013), such as in amputees with phantom limbs. These findings underline the importance of the embodiment constraint, where prolonged manipulation of the spatiotemporal coherence of bodily signals can reshape the boundaries of the peripersonal space. The interaction between the embodiment and the peripersonal constraint thus allows a flexible, however, temporally graded updating of the body

representation via a manipulation of the internal model of the body by prolonged multisensory input (Tsakiris, 2010).

1.1.2 Pathologically altered body representations

In contrast to body illusions in healthy persons, altered body perception in various neurological conditions is prominent without having to establish a multimodal conflict or can occur spontaneously (stimulus-independent). In somatoparaphrenia, for instance, the patients show delusional misidentification and confabulations related to contralesional body-parts such that the patient believes that his or her own leg belongs to his/her spouse (Feinberg & Venneri, 2014). Tsakiris (2010) proposed that body illusions further depend on already existing (stimulus-independent) *internal body representations*. The need of internal body representations becomes evident in amputees with spontaneous phantom phenomena (de Preester & Tsakiris, 2009) or in body descriptions within dream reports (Bekrater-Bodmann et al., 2015), where the perception of the body can be incongruent with the physical body.

To conclude, the model of Blanke et al. (2015) and the model by Tsakiris (2010) can provide a fruitful theoretical framework for the consideration of the origins and contextual determinants of altered body perception (phantom phenomena) in amputees such as a referral of sensations to a missing limb when the body is stimulated (section 1.2) or the manipulation of phantom perception within body illusion experiments (Hunter, 2003) (section 1.3). The model by Tsakiris (2010) emphasizes the role of internal body representations, which is important to consider in clinical populations. These models are of particular importance when trying to improve stimulus configurations for normalizing distorted neural representations of the body (Senkowski & Heinz, 2016).

1.1.3 Primary sensorimotor representations of the body

Penfield and Boldrey (1937) systematically investigated the primary somatosensory and motor representations of the body in response to intra-cortical stimulation of different sites of the primary somatosensory (SI) and primary motor cortex (M1) in humans. These investigations offered two major insights: (1) the body is topographically represented in the contralateral or both ipsi- and contralaleral brain hemisphere, for example, the arm adjacent to the hand representation (somatotopic maps) (2) body parts revealing higher sensitivity or musculature that requires more

fine-grained motor control show larger representations in these somatosensory or motor maps (homuncular representation) (Purves et al., 2008a, 2008b; Tamura, Shibukawa, Shintani, Kaneko, & Ichinohe, 2008) (**Fig. 2**). Somatotopic maps have also been identified in other structures like the secondary somatosensory cortex, the thalamus (Churchill, Arnold, & Garraghty, 2001; Hong, Kwon, & Jang, 2011; Jones & Pons, 1998; Yamada et al., 2007), the cerebellum (Takanashi et al., 2003), & the brainstem (Churchill et al., 2001; Marx et al., 2005).
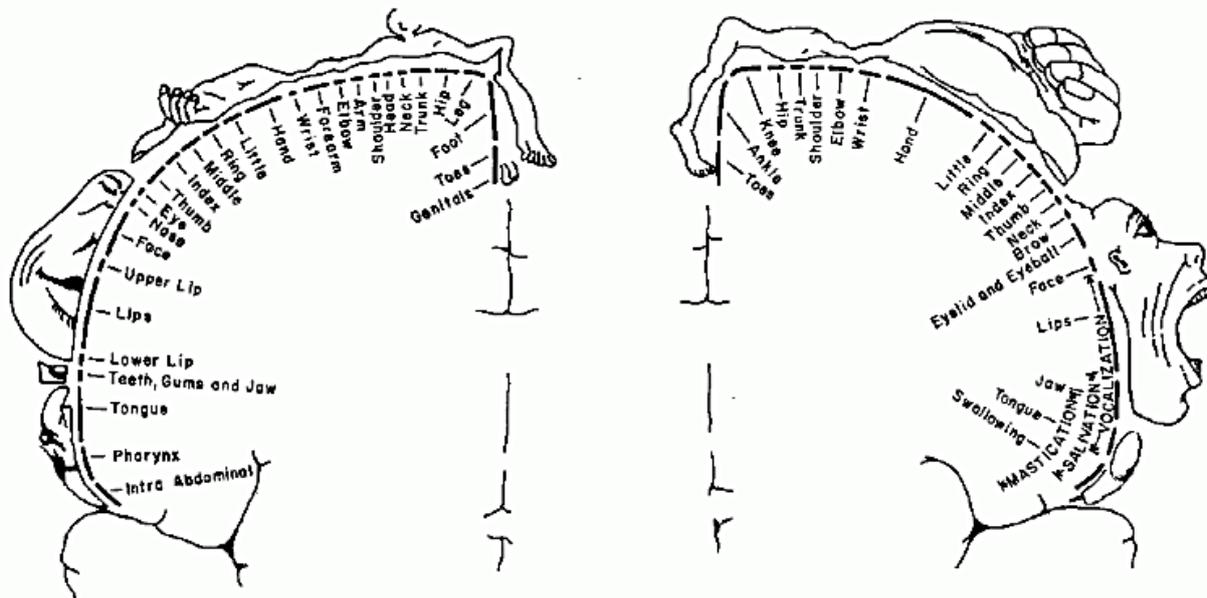
Figure 2 Penfield somatosensory (left) and motor (right) homunculi. Penfield showed that the body is topographically represented in the contralateral primary somatosensory (left) and primary motor (right) cortex with disproportional representation sizes corresponding to the complexity of sensory and motor functions of respective body parts. The topographic maps shown by Penfield and colleagues have been revised. Reprinted from Penfield, W., & Rasmussen, T. (1950). *The Cerebral Cortex of Man*. New York, NY: Macmillan Company.

1.1.4 Higher-order neural body representations

The motor action of scratching an irritated skin site not only depends on somatotopic maps but rather on a spatiotopic map. For an adequate motor response, the skin-centered reference frame has to be remapped to localize the stimulus in an egocentric extrapersonal space referring to proprioceptive or visual cues (Azañón & Soto-Faraco, 2008). The remapping of unisensory maps to a common frame of reference, providing a coherent perception of the self in relation to the world, has been discussed to be dependent on brain regions with multimodal neurons like those

found in the premotor and posterior parietal cortices or in the posterior insula (Apps, Tajadura-Jiménez, Sereno, Blanke, & Tsakiris, 2015; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981a, 1981b). Transcranial magnetic stimulation over the right posterior parietal cortex, for instance, has been shown to selectively diminish integration of proprioceptive and tactile information and thereby the ability to localize touch on the skin at varying body postures (Azañón, Longo, Soto-Faraco, & Haggard, 2010).

The multisensory receptive fields reveal a coarse spatial resolution generally covering whole body parts like the arm or even the entire body and can even extend over the body boundaries (peripersonal space) (Rizzolatti et al., 1981a, 1981b; Stein & Stanford, 2008). Thus, multimodal receptive fields offer the opportunity of integrating different unimodal frames of reference into a common, for example, arm-centered reference frame to allow enhanced processing. These fronto-parietal areas with multimodal receptive fields have been shown to be strongly interconnected (Mars et al., 2011; Tomassini et al., 2007; Uddin et al., 2010; Uddin, Kaplan, Molnar-Szakacs, Zaidel, & Iacoboni, 2005). Thus, it is more appropriate to talk about a fronto-parietal network. Various body part (e.g., the rubber hand illusion) and full-body illusions have been shown to be related to activation in this fronto-parietal network (Ehrsson, Spence, & Passingham, 2004; Ehrsson, Holmes, & Passingham, 2005). The rubber hand illusion, for example, has been shown to be linked to brain activity in the ventral premotor cortex and the intraparietal sulcus and the strength of the illusion correlated positively with brain activity in the ventral premotor cortex and the cerebellum (Ehrsson et al., 2005, 2004). A recent meta-analysis by Grivaz et al. (2017) found a widespread fronto-parietal network to be co-activated in studies either investigating multimodal integration in peripersonal space (the space surrounding the perceived body) or body illusions affecting ownership sensations.

1.2 Phantom phenomena in amputees

One might assume that the amputation or deafferentation of a body part is accompanied by an immediate disembodiment from that body part. However, most patients continue to perceive their missing or deafferented limb as a phantom (Sherman, Arena, Sherman, & Ernst, 1989; Sherman, Sherman, & Parker, 1984). Nearly all amputees experience perceptual phenomena that are paradoxically allocated to the missing limb (Jensen, Krebs, Nielsen, & Rasmussen, 1985; Kooijman

et al., 2000; Sherman, 1995). These phantom phenomena comprise a general awareness of the existence of the missing body part as one's own, lacking a specific sensory quality (phantom awareness) or more specific non-painful somatic sensations (phantom sensations) (Hunter et al., 2003) such as tingling, itching, pressure, movement, warmth, cold. Moreover, some amputees describe a telescoping phenomenon, which is the sensation that the phantom limb has changed its length, most often shortened (Sherman, 1997). Phantom awareness can occur without any specific phantom sensations, while phantom sensations are always accompanied by phantom awareness (Hunter et al., 2003; Hunter, Katz, & Davis, 2008). Phantom phenomena can be spontaneous (stimulus-independent) or elicited by a sensory stimulus (e.g., tactile stimulation at the stump), termed evoked phantom sensation (Sherman, 1997). Phantom pain is a common consequence of amputation or deafferentation and is defined as the experience of pain allocated to the amputated body part, which is reported to occur in about 60-80% of the cases (Carlen, Wall, Nadvorna, & Steinbach, 1978; Jensen et al., 1985). Often, the perceptual features of the phantom pain resemble those of pain experiences prior to the amputation (Katz & Melzack, 1990). It is important to distinguish phantom phenomena from painful and non-painful residual limb phenomena, which are percepts related to the body part adjacent to the amputation or deafferentation line (Sherman, 1997).

1.2.1 Etiology of painful and non-painful phantom phenomena

The pathophysiology and etiology of painful and non-painful phantom phenomena is not well understood (Flor, Nikolajsen, Jensen, & Staehelin Jensen, 2006; Weeks, Anderson-Barnes, & Tsao, 2010). Peripheral and central factors have been discussed to contribute to the experience of phantom pain (Devor, 2005; Flor et al. 2006). It is important to note that peripheral contributions are not sufficient to explain phantom pain. For instance, local anesthesia of the residual limb (Nyström & Hagbarth, 1981), the plexus innervating the stump (Birbaumer et al., 1997), was not sufficient to eliminate phantom pain in all amputees. However, reorganization takes also place at the level of the dorsal root ganglion, potentially also contributing to the phantom pain. But epidural and spinal anesthesia were also not sufficient to eliminate habitual phantom pain in all amputees (Baron & Maier, 1995), emphasizing the role of central factors for the experience of phantom pain (Flor et al. 2006).

Phantom pain does not occur in isolation, but often in combination with pain in the residual limb or other body parts such as the intact limb, the neck or the back (Desmond & MacLachlan, 2010; Ephraim, Wegener, MacKenzie, Dillingham, & Pezzin, 2005; Hanley et al., 2009). In accordance with other chronic pain syndromes, psychological factors like anxiety or depression have been shown to modify the course and severity of phantom pain, however, they are not the cause of phantom pain (Ephraim et al., 2005; Hill, 1999). For instance, amputees suffering from phantom pain exhibit reduced physical and health-related quality of life (Taghipour et al., 2009), poorer coping with the limitations associated with the amputation (Giummarra et al., 2011) and show maladaptive coping strategies like pain-related catastrophizing (Buchheit et al., 2015; Vase et al., 2011).

Flor et al. (1995) found a strong positive relationship between the magnitude of phantom pain and the amount of SI reorganization, but neither non-painful phantom phenomena nor stump pain were related to cortical reorganization. These findings have been replicated in other studies (Flor et al., 1998; Grüsser et al., 2001, 2004; MacIver, Lloyd, Kelly, Roberts, & Nurmikko, 2008) and have also been demonstrated in M1 (Karl, Birbaumer, Lutzenberger, Cohen, & Flor, 2001; Lotze, Flor, Grodd, Larbig, & Birbaumer, 2001a; Raffin, Richard, Giraux, & Reilly, 2016). The association between topographic shifts in SI and the magnitude of pain has also been shown in other chronic pain syndromes like complex regional pain syndrome (Vartiainen et al., 2008), chronic back pain (Flor, Braun, Elbert, & Birbaumer, 1997) or unilateral pain following a herpes simplex infection (Vartiainen et al., 2009).

Several factors have been discussed to facilitate these reorganizational shifts in SI. These factors include (1) abnormal-noisy input arising from ectopic activity (abnormal discharges) in residual limb neuroma (terminal swelling in the residual limb, which is also characterized by axonal sprouting) (Soin, Fang, & Velasco, 2015) or the dorsal root ganglion (Katz, 1992), (2) loss of inhibitory C-fiber input, as C-fibers have been discussed to have a stabilizing function for cortical maps (Calford & Tweedale, 1991), (3) long-lasting pre-amputation pain as well as pain immediately before the amputation (Flor, 2000, 2012; Weeks et al., 2010) and (4) psychological variables like anxiety, depression (Ephraim et al., 2005; Hill, 1999; Raichle et al., 2015), maladaptive coping with pain (Giummarra et al., 2011) or pain catastrophizing (Vase et al., 2011) (**Fig. 3**).

However, there is a need to quantify the contribution of these central, peripheral and psychological factors within longitudinal studies to enable distinction between factors that are antecedents or consequences of phantom and residual limb pain (Weeks et al., 2010). Moreover, the role of other brain regions known to be important for appetitive and aversive learning or affective processing might play a role for the chronification of phantom pain (Moseley & Flor, 2012). For instance, in hypnotically induced phantom pain in upper-limb amputees, ratings of the intensity of phantom pain have been shown to be significantly positively correlated with activity in the anterior and posterior cingulum as assessed by positron emission tomography (Willoch et al., 2000).
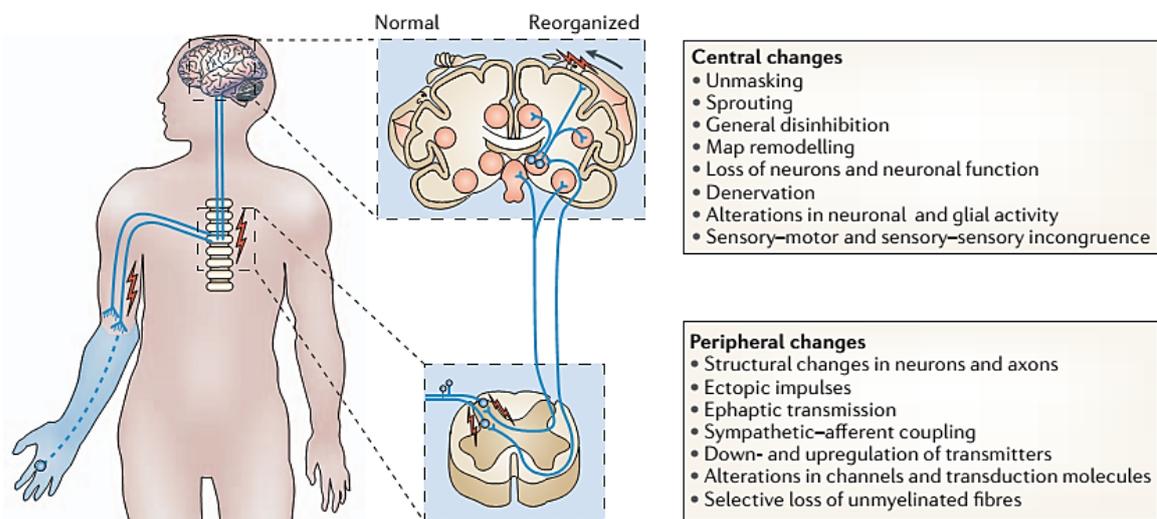
Figure 3 Illustration of the diversity of functional and structural, peripheral and central alterations along the neuraxis post-amputation. Figure reprinted from Flor et al. (2006).

1.2.2 The neural correlates of non-painful phantom phenomena

Based on findings of massive topographical reorganization in SI following dorsal rhizotomies in macaques (Pons et al., 1991), Ramachandran et al. (1992) proposed that painful- and non-painful phantom phenomena might be a direct consequence of this cortical remapping. The authors found that stimulation of the face area, which is adjacent to the upper-limb representation in SI, elicited referrals allocated to the phantom limb with a one-to-one topographical correspondence between individual stimulation sites in the face and the phantom limb. Some authors proposed that this cortical reorganization might have an adaptive (i.e., pain-preventive) function (Merzenich et al., 1984; Ramachandran et al., 1992). Multiple lines of evidence,

however, indicate that painful, but not non-painful phantom phenomena – such as non-painful evoked phantom sensations – are related to topographic shifts in primary sensorimotor body representations (Bolognini, Olgiati, Maravita, Ferraro, & Fregni, 2013; Grüsser et al., 2004).

Flor et al. (1995) found a significant positive relationship between the magnitude of phantom pain and the amount of SI reorganization, but neither non-painful phantom phenomena nor stump pain were related to cortical reorganization using neuromagnetic imaging in upper-limb amputees. These findings have been replicated in other studies (Flor et al., 1998; Grüsser et al., 2001, 2004). For instance, Grüsser et al. (2001) found a significant positive relationship between painfully elicited painful referred sensations, habitual phantom pain and cortical reorganization in SI as assessed by neuroelectric source imaging. However, non-painful phantom phenomena, such as non-painful evoked phantom sensations, were not linked to cortical reorganization in SI. While phantom pain has been shown to be associated with topographic reorganization in SI and M1, the topography of body sites capable of eliciting phantom sensations often follows a spatial pattern that cannot readily be explained by topographic reorganization in SI. Various studies have shown that phantom sensations can often be elicited from body sites that are remote in terms of both anatomy and cortical representation in SI (Borsook et al., 1998; Giummarra et al., 2011; Grüsser et al., 2001, 2004; Knecht, Henningsen, et al., 1996). Moreover, in patients with spinal cord injury, Moore et al. (2000) could induce referred sensations projected to the chest at the level of the spinal cord injury by stimulating the forearm. The authors observed activation in brain areas corresponding to the representation of the forearm and the chest, which were segregated by centimeters of nonresponsive cortex in SI. It was proposed that non-painful phantom phenomena, including non-painful evoked phantom sensations, might rely on brain regions other than SI (Flor et al., 2000). Grüsser et al. (2004) investigated two upper limb amputees in whom phantom sensations could be evoked at remote body sites at the ipsi and contralateral leg. While the authors found topographical shifts in the representation the mouth in the deafferented hemisphere, no reorganization was observed in the feet representation from which phantom sensations could be elicited. These finding indicate that painful, but not non-painful phantom phenomena are related to topographic reorganization in SI. Candidate brain structures that have been

discussed by the authors and others (Flor et al., 2000) are the secondary somatosensory cortex, which shows a higher reorganizational potential and different topography than SI, and the posterior parietal cortex (i.e., the intraparietal sulci), which has been shown to be important for the coherent multimodal perception and localization of body parts (Apps et al., 2015; Avillac, Ben Hamed, & Duhamel, 2007).

A potential role of posterior parietal regions for the perception of non-painful phantom phenomena is indicated by studies using neuromodulation techniques. For instance, cathodal transcranial direct current stimulation over the posterior parietal cortex temporally diminished non-painful phantom phenomena without affecting phantom pain, while anodal (depolarizing) stimulation over the motor cortex induced short-term reduction of phantom pain – with no alterations in non-painful phantom sensations (Bolognini et al., 2013). Based on their findings the authors suggested that non-painful phantom phenomena might be linked to hyperexcitability in the posterior parietal cortex.

A recent fMRI-study with five upper and lower limb amputees and matched healthy controls, showed a distributed network comprising the ventral inferior cortex (BA44/45), the intraparietal sulci, the inferior parietal lobes and the secondary somatosensory cortices to be associated with non-painful phantom sensations (Andoh et al., 2017). However, the sample of Andoh *et al.* (2017) was heterogeneous by including upper- and lower limb amputees and evoked phantom sensations were elicited at the residual limb and remote body sites.

Appenzeller and Bicknell (1969) reported on two lower-limb amputees who later experienced stroke with significant impairments in haptically identifying objects (stereognosis). Stereognosis has been shown to be dependent on the processing in posterior parietal cortex (Knecht, Kunesch, & Schnitzler, 1996). Importantly, these patients reported perceiving non-painful phantom limbs that disappeared following stroke. These anecdotal reports indicate an important role of the posterior parietal cortex in the perception of non-painful phantom phenomena. Furthermore, reports on perceiving extra limbs (supernumerary limbs) in various neurological populations including stroke-patients (Srivastava et al., 2008) or patients with epileptic seizures (Millonig, Bodner, Donnemiller, Wolf, & Unterberger, 2011) point towards a causal contribution of the posterior parietal (cf., Millonig et al., 2011).

1.2.3 Mirror visual feedback illusions in the treatment of phantom limb pain

In mirror visual feedback illusions, movements of the affected limb are visually recreated by movements of the contralateral limb (Deconinck et al. 2014). Ramachandran et al. (1992) originally described mirror illusions in amputees suffering from phantom pain. The authors positioned a mirror mid-sagittal in front of the amputee so that the intact limb visually superimposed the amputated limb and the amputee performed movements with his or her intact limb. The authors found an alleviation of phantom pain and a relief of spasms in the phantom in a proportion of the patients. A randomized placebo-controlled study by Chan et al. (2007) showed that four weeks of mirror training led to the alleviation of phantom pain in a proportion of lower-limb amputees, whereby simple movement training, without a mirror, or motor imagery training was ineffective. The study by Chan et al. (2007) was conducted with some patients with recent leg amputation. Thus, their results have to be validated in chronic amputees since spontaneous recovery from pain has been reported in sub-acute phantom pain (Schley et al., 2008).

In accordance with the topographic alterations in the primary sensorimotor cortex found in various neuropathic pain conditions (see section 1.2), it has been proposed that a re-establishment of congruent input into the sensorimotor representation of the affected limb might be the neural correlate of successful mirror visual feedback interventions (Foell et al. 2011; Deconinck et al. 2014). Foell et al. (2014) used a 4-week mirror training in a sample of upper-limb amputees. The authors showed that mirror therapy was associated with a reduction in pain and accompanying reversal of topographic reorganization in SI (Foell et al., 2014). However, a reversal of cortical reorganization and a reduction in phantom pain was only observed in amputees without telescoping (section 1.2). These findings emphasize the role of body representations under the perspective of the interplay between non-painful and painful phantom phenomena.

2 GOALS AND HYPOTHESES

Study 1

Study 1 investigated if a novel mirror visual feedback device (the mirror glasses) could induce mirror illusions in healthy volunteers. Therefore, the self-reported capacity for mirror illusions and the neural circuitry was compared between the novel mirror glasses and the well-established mirror box in a within-subjects design in counterbalanced order in the MRI-scanner. The conceptual difference between both mirror devices is seeing both hands moving in synchrony with the mirror box and seeing only the mirror reflection of the actual moving limb with the mirror glasses.

As discussed in section 1.2, the recruitment of the sensorimotor representation of the non-mirrored limb has been reported in several studies using mirror visual feedback in healthy subjects and has been discussed to be the neural correlate of effective mirror therapy (Deconinck et al., 2014; Diers, Christmann, Koeppe, Ruf, & Flor, 2010; Matthys et al., 2009). Moreover, motor mirror visual feedback tasks have been reported to be linked to other brain regions including the primary sensorimotor representation of the actually moving limb, the secondary somatosensory and premotor cortex, supplementary motor area, the ipsilateral cerebellum and lateral occipital regions (Diers et al., 2015, 2010; Matthys et al., 2009). Seeing the actually moving limb in addition to the mirror reflection of the moving limb has been discussed to potentially reduce the capacity for a mirror illusion by distracting attention from the mirror reflection (Deconinck et al., 2014; Hadoush, Mano, Sunagawa, Nakanishi, & Ochi, 2013). A magnetoencephalographic study with healthy subjects found increased excitability in the sensorimotor cortex corresponding to the non-mirrored limb when the view on the actually moving limb was occluded compared to seeing both hands in a classical mirror box setup (Hadoush et al., 2013). While consistent brain activation has been reported during mirror visual feedback, little is known about interactions (connectivity) between different brain regions during mirror illusions and thus about the neural networks underlying mirror illusions (Deconinck et al., 2014). It has been proposed that mirror visual feedback is associated with a reduction of interhemispheric inhibition from the contralateral to the ipsilateral hemisphere in primary sensorimotor areas (Läppchen et al., 2012; Nojima et al., 2012; Nojima, Oga, Fukuyama, Kawamata, & Mima, 2013).

The main hypotheses of Study 1 were as follows:

H 1: The self-reported capacity for a mirror illusion is significantly higher in the mirror glasses versus the mirror box condition.

H 2: The representation of the non-mirrored limb in the primary sensorimotor cortex is significantly activated in the mirror glasses and mirror box conditions.

H 3: The actual movement of a limb yields significant activation in the primary sensorimotor cortex representing the physically moving limb, the secondary somatosensory and premotor cortices, the supplementary motor area, the ipsilateral cerebellum and lateral occipital regions in the mirror glasses and mirror box conditions.

H 4: The primary sensorimotor cortex representing the non-mirrored limb is significantly higher activated in the mirror glasses than the mirror box condition.

H 5: The mirror box and mirror glasses illusion is related to significantly increased interhemispheric task-dependent connectivity between the primary sensorimotor hand representations.

Study 2

Study 2 sought to assess the neural circuitry of evoked non-painful phantom sensations in upper-limb amputees using fMRI. The topography of body sites from which non-painful evoked phantom sensations can be elicited in amputees has been frequently described to follow a pattern that cannot readily be explained by topographic reorganization in SI (section 1.2) (Andoh et al., 2017; Borsook et al., 1998; Grüsser et al., 2004; Knecht, Henningsen, et al., 1996). Often phantom sensations could be elicited from body sites, which are contralateral or remote with respect to the deafferentation line and the representation of the former limb in SI. Phantom sensations elicited at body sites remote from the residual limb can be explained by reorganization in the secondary somatosensory cortex, showing a different topography and a higher reorganizational potential than SI. Non-painful phantom sensations have been discussed to be related with activation in ventral frontal and posterior parietal regions (section 1.2).

The main hypotheses of Study 2 were as follows:

H 1: The topography of body sites eliciting phantom sensations follows a pattern, which cannot readily be explained by topographic reorganization in SI, including elicitation sites remote and contralateral with respect to the former limb representation in SI.

H 2: The perception of evoked phantom sensations is related to significant activation in brain regions with multimodal neurons including the premotor, insular, and posterior parietal cortices.

H3: The perception of evoked phantom sensations is related to significant activation in the secondary somatosensory cortex.

H 4: The perception of evoked phantom sensations is associated with increased fronto-parietal connectivity.

3 EMPIRICAL STUDIES

Study 1

Do mirror glasses have the same effect on brain activity as a mirror box? Evidence from a functional magnetic resonance imaging study with healthy subjects [1]

Abstract

Since its original proposal, mirror therapy has been established as a successful neurorehabilitative intervention in several neurological disorders to recover motor function or to relief pain. Mirror therapy seems to operate by reactivating the contralesional representation of the non-mirrored limb in primary motor- and somatosensory cortex. However, mirror boxes have some limitations which prompted the use of additional mirror visual feedback devices. The present study evaluated the utility of mirror glasses compared to a mirror box. We also tested the hypothesis that increased interhemispheric communication between the motor hand areas is the mechanism by which mirror visual feedback recruits the representation of the non-mirrored limb. Therefore, mirror illusion capacity and brain activations were measured in a within-subject design during both mirror visual feedback conditions in counterbalanced order with 20 healthy subjects inside a magnetic resonance imaging scanner. Furthermore, we analyzed task-dependent functional connectivity between motor hand representations using psychophysiological interaction analysis during both mirror tasks. Neither the subjective quality of mirror illusions nor the patterns of functional brain activation differed between the mirror tasks. The sensorimotor representation of the non-mirrored hand was recruited in both mirror tasks. However, a significant increase in interhemispheric connectivity between the hand areas was only observed in the mirror glasses condition, suggesting different mechanisms for the recruitment of the representation of the non-mirrored hand in the two mirror tasks. We conclude that the mirror glasses might be a promising alternative to the mirror box, as they induce similar patterns of brain activation. Moreover, the mirror glasses can be easy applied in therapy and research. We want to emphasize that the neural mechanisms for the recruitment of the affected limb representation might differ depending on conceptual differences between MVF devices. However, our findings need to be validated within specific patient groups.

Keywords: mirror therapy, mirror visual feedback, phantom limb pain, stroke, complex regional pain syndrome, functional magnetic resonance imaging, primary somatosensory cortex, primary motor cortex, mirror box, rehabilitation

Introduction

The idea of using altered visual feedback to relieve phantom limb pain by using a mirror box (MB) was originally proposed by Ramachandran et al. (Ramachandran et al., 1992). Since then mirror visual feedback (MVF) has been established in the treatment of phantom limb pain (Chan et al. 2007; Moseley et al. 2008; Foell et al. 2014), but also as an important therapeutic tool for functional recovery after a stroke (Sathian, Greenspan, & Wolf, 2000; Sütbeyaz, Yavuzer, Sezer, & Koseoglu, 2007; Yavuzer et al., 2008), physiotherapy after wrist fracture (Altschuler & Hu, 2008), the treatment of complex regional pain syndrome (McCabe et al., 2003; McCabe, Haigh, & Blake, 2008) or for reinstating body ownership in somatoparaphrenia (Fotopoulou et al., 2011).

The basic idea of MVF is that extended viewing of movements of the unaffected limb visually superimposed on the affected limb by a sagittally placed mirror triggers the perception that the phantom (or affected) limb is moving (Ramachandran & Rogers-Ramachandran, 1996). Whereas the beneficial effects of MVF have been repeatedly demonstrated, the mechanisms underlying MVF-induced improvements in motor function and pain relief remain unclear (Deconinck et al., 2014; Nojima et al., 2012). There is increasing evidence that a reactivation of the affected limb representation in the sensorimotor strip and accompanying neuroplasticity is an important neural correlate of the MVF related neurorehabilitation (Deconinck et al., 2014; Diers et al., 2015, 2010). However, it remains unclear how the sensorimotor representation of the non-mirrored (affected) limb becomes functionally recruited because studies examining the functional connectivity between brain areas during MVF are still rare (Deconinck et al., 2014; Läppchen et al., 2012).

In the MB approach, the (affected) limb is positioned behind a mirror, which is oriented along the observer's midline so that the visual reflection of a moving (intact) limb visually replaces the hidden (affected) limb. Using a MB in therapy and research is constrained by several technical and conceptual limitations such as size and weight, which reduces the degrees of freedom for possible movements in front of the mirror and constrains its applicability in therapy and in magnetic resonance imaging (MRI) setups (Walsh & Bannister, 2010). In contrast, mirror glasses (MG) limit the field of view to the visual reflection of the moving (intact) limb which replaces the hidden (affected) limb in the visual field whereby the actually moving limb is visually

occluded. This is achieved by covering the eye ipsilateral to the movement and mirroring the visual hemifield to the other eye. It has been proposed that seeing the actual moving hand, in addition to the visual reflection of the moving hand, might be an irrelevant distractor reducing the ability of the subject to stay focused on the reflection of the moving hand (Hadoush et al., 2013; Walsh & Bannister, 2010). Thus MG might have a higher capability of recruiting the motor representation ipsilateral to the moving hand (further referred to as MI_{ipsi}) compared to MB by enabling increased spatial attention towards the reflection of the moving (affected) limb (Hadoush et al., 2013). MG deliver a more realistic image of the mirrored limb than virtual reality systems, which has been shown to be an important aspect of perceiving body illusions (Tsakiris, Schuetz-Bosbach, & Gallagher, 2007). Additionally, MG are smaller in size and weight than the MB. Thus MG might be more attractive for healthcare providers and more appropriate in functional MRI (fMRI) paradigms (Walsh & Bannister, 2010). Compared to other studies, which focused on classical or virtual applications of the MB (Diers et al., 2015, 2010; Michielsen et al., 2011), this is the first study systematically investigating the subjective quality and associated functional brain activity provided by MG which limit the field of view to the visual reflection of the moving (intact) limb.

To evaluate the efficiency of MG, we examined 20 healthy subjects in a counterbalanced within-subjects design with MVF provided either by MB or MG. We assessed ratings on the intensity and vividness of mirror illusions as well as fMRI data. Due to the putatively distracting effect of seeing the moving hand in addition to the visual reflection of the moving hand, we hypothesized to find higher subjective mirror illusion capacities as well as an increased recruitment of MI_{ipsi} in the MG compared to the MB condition. Moreover, we analyzed task-dependent functional connectivity between both hand areas, as one proposed neural mechanism for the recruitment of the sensorimotor representation corresponding to the hidden (affected) limb (Deconinck et al., 2014).

Methods

Participants

Twenty healthy subjects ($M = 31.3$ years, $SD = 7.7$ years; 15 females) took part in the study. Participants were right handed as assessed with the Edinburgh Handedness

Inventory (Oldfield, 1971), reported normal or corrected-to-normal vision, had no history of neurological disease and did not use any centrally acting medication such as opiates. We first wanted to evaluate the effects of MG in a group of healthy subjects before using this device in specific patient groups.

Ethics Statement

The participants gave written informed consent in accordance with the Declaration of Helsinki (2008) prior to participation. The study was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University (internal reference: 2008-336N- MA).

Mirror Glasses

The MG (Scottish Health Innovations Limited, Glasgow, Scotland) can be used within a MRI environment due to the absence of any ferromagnetic components. The MG limit the field of view to the visual reflection of the moving limb by reflecting the field of view to the eye contralateral to the moving limb. In our setup the field of view was restricted to the mirror reflection of the moving right hand (visually appearing as left hand) which was seen through the right eye (Fig. 1). In contrast, the MB provides a view of the actual moving limb together with the visual reflection of the moving limb appearing to move in synchrony. Furthermore, the MG has a larger field of view compared to the MB, including the entire half of the body with its natural range of movements (Fig. 1).
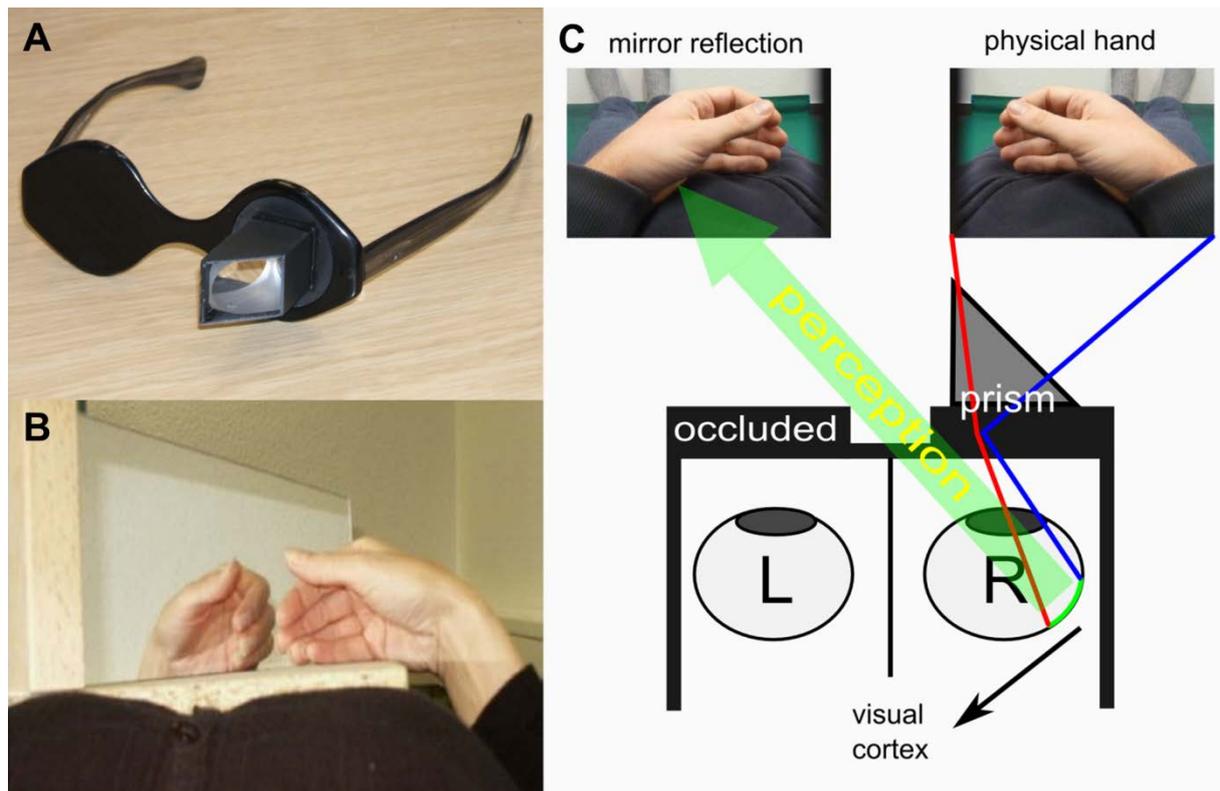
Fig. 1. Mirror visual feedback (MVF) devices. A Mirror glasses: are usable within an MR environment. The optical path was deflected by a prism, which was a 1.5-1.53 45-90-45 angled glass, Barium crown (BK-7, Abbe 63) with quarter wavelength surface tolerance. **B** Mirror box: was a framed glass mirror (size: 35 by 12 centimetres / 13.8 by 4.7 inches) which was placed on the abdomen of the subject providing view on the executing hand as well as the visual reflection of the hand appearing to move in synchrony. During both conditions view on the mirror reflection of the moving limb was provided by means of an additional mirror attached to the head coil. (C) Illustration of the MVF as provided by the mirror glasses: in contrast to the mirror box the users' view is limited to the mirror reflection of the moving (physical) hand as opposed to seeing both hands (physical hand and visual reflection of the physical hand). The mirror reflection of the physical hand was seen through on eye by means of a prism leading to a total inversion in the left-right dimension (in our setup the right hand movements were seen through the right eye appearing as left hand movements). Furthermore, mirror glasses provide a much larger field of view, allowing the whole limb to be inverted.

Experimental procedure

The participants were tested in a counterbalanced within-subjects design for the two conditions MB and MG inside the scanner. In the MG condition, participants wore MG, during the MB condition a MB was placed on the abdomen of the subject, enabling them to view the mirrored right hand (appearing as left hand) as well as the actual right hand (Fig. 1). In both MVF conditions participants were instructed to repeatedly close and open their right hand at a frequency of 1 Hz as paced by an auditory signal presented via earphones. During movement trials participants were instructed to focus on the visual reflection of the moving right hand. Participants kept their left hand immobile and out of view in a comfortable position on their abdomen. During the experiment the participants view was redirected using a mirror attached to the MRI head-coil. This way, they could easily observe the upper half of the body including the actual or illusory limb movements.

Subjective ratings on mirror illusions

After each MVF condition, the intensity and vividness of mirror illusions were verbally assessed using a seven-point numeric rating scale. The scale ranged from 1 ('as clear and vivid as a real perceptual experience') to 7 ('not at all clear and vivid') and was modeled after the Questionnaire upon Mental Imagery (Sheehan, 1967). The questions have been used in previous studies (Diers et al., 2015, 2010; Lotze, Flor, Grodd, Larbig, & Birbaumer, 2001b). Mirror illusion items were: Did you feel that the movement of the displayed hand belonged to your left hand? (Vividness) How clearly did you feel the movement of your left hand? (Intensity).

MRI data acquisition

During execution of both MVF tasks, a Siemens 3 T MAGNETOM Trio whole-body scanner (Siemens AG, Erlangen, Germany) was used in combination with a 12-channel radio-frequency head coil to obtain eighty whole-brain T_2*-weighted gradient-echo echo planar imaging (EPI) volumes with blood related oxygen level-dependent contrast [repetition time (TR) = 3.3 s; echo time (TE) = 45 ms; flip angle (α) = 90°]. Imaging volumes consisted of 40 slices angulated in parallel to the anterior commissure-posterior commissure with a gap of 0.69 mm recorded in ascending order. Each slice had a matrix size of 96 x 96 voxels with an anisotropic voxel-size of 2.3 x 2.3 x 2.9 mm. For each MVF condition, participants were tested in an

alternating block design consisting of six blocks of right-hand movements interspersed by seven baseline blocks. Each block consisted of six scans. Both conditions were split into two separate sessions of about five minutes separated by a five-minute break.

Within the same session, a T_1-weighted scan (160 contiguous slice, matrix size 240 x 256 voxels, voxel-size = 1 x 1 x 1.1 mm) was conducted to collect a high-resolution structural volume for anatomical reference. The magnetization-prepared rapid acquisition gradient-echo sequence was employed with TR = 2.3 s, TE = 2.98 ms, and α = 9°.

Statistical analysis of fMRI data

The MRI data were analyzed using tools from FMRIB's Software Library (FSL) version 5.02 (Smith et al., 2004). The first five EPI volumes were discarded prior to preprocessing to account for T1-equilibration effects. Prior to statistical estimation, the following preprocessing steps were subjected: Intramodal motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), spatial smoothing using an isotropic Gaussian kernel of 5 mm (full width at half maximum), mean-based intensity normalization of all volumes, and high-pass temporal filtering (σ = 100 s). Registration was performed in 2-steps: EPI volumes were first spatially realigned to the high-resolution T1-weighted volume, where non-brain structures were removed using Brain Extraction Tool (BET) (Smith, 2002). EPI images were then registered to the standard MNI152 space (Montreal Neurological Institute, Montreal, Canada) using non-affine FNIRT-registration (Andersson, Jenkinson, & Smith, 2007) with a warp-resolution of 8 mm. Time-series statistical analysis was carried out using the prewhitening tool FMRIB's Improved Linear Model (FILM) with local autocorrelation correction.

Functional MRI statistical analysis was carried out using fMRI Expert Analysis Tool (FEAT) (Smith et al., 2004). Data from each subject and session (MG; MB) were analyzed at a first-level of analysis. Trials of performing the MVF tasks were used as one factor of interest and convolved with a double-gamma function to model the hemodynamic response function and were entered as a predictor into a general linear model. To account for movement-related artifacts in the signal, the six rigid-body movement parameters were additionally included as nuisance regressors in the

25

design matrix. Brain areas were identified based on the FSL Harvard-Oxford Atlas (Eickhoff et al., 2007)

Inter-session (MG > MB and MB < MG) and group analyses were carried out using FMRIB's Local Analysis of Mixed Effects (FLAME) (Mark W Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Areas of significant fMRI activations associated with both MVF conditions were calculated by entering the first-level (sessions) statistics into a second-level mixed-effects group analysis. To compare brain activations between both MVF conditions, we contrasted both MVF sessions (MG > MB and MG < MB) for each subject within a fixed-effects analysis, which was subsequently entered into a third-level mixed-effects group analysis. Areas of significant fMRI response were determined using clusters identified by a $z > 3.0$ threshold and a corrected cluster threshold of $p = 0.05$ assuming a Gaussian random field for the z-statistics.

Psychophysiological interaction analysis (PPI)

Psychophysiological interaction (PPI) analysis is a method to estimate task-dependent functional connectivity among brain regions (Friston et al., 1997; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). The PPI analysis was conducted to specifically address the hypothesis of increased interhemispheric interaction between both MI hand areas during both MVF conditions as a modulating factor of the recruitment of MI_{ipsi} corresponding to the non-mirrored hand as proposed in prior literature (Deconinck et al., 2014). For that purpose, the deconvolved voxel time courses of each subject and session were extracted from the native space coordinates of peak voxels within the contralateral MI (MI_{contra}) as revealed by the t-contrasts of the first-level analyses of both MVF conditions. We chose MI_{contra} because it was consistently activated in all subjects during both MVF. The fMRI time course of each selected region of interest (ROI) was obtained by using the first eigenvariate of a radial sphere of 5 mm surrounding each peak voxel. Based on the individual voxel time series, statistical parametric maps for each subject and MVF condition were created, representing regions in which the fMRI signal was predicted by the PPI term (the cross product of the physiological and the psychological factors) (Friston et al., 1997). Both the physiological and psychological factors were included in the design matrix as confounding variables. Furthermore, we include the white matter- and cerebrospinal fluid-signal as nuisance regressors (O'Reilly et al., 2012).

The first-level (session) statistics were entered into a second-level group statistic to reveal task-dependent functional connectivity for both MVF conditions. Z (Gaussianized T) statistic images were thresholded using a cluster-based threshold of $z > 3.0$ and a whole-brain corrected cluster significance threshold of $p = 0.05$.

Analysis of subjective ratings

The seven-point-ratings on the intensity and vividness of mirror illusions during both MVF conditions were analyzed by SPSS Statistics 20.0.0 software (IBM Corporation, New York, USA). Comparisons of the two mirror illusions items between conditions were conducted using paired sample t-tests with Bonferroni adjusted alpha-levels of 0.025 (0.05/2).

Results

Ratings on mirror illusions

The participants did not report any problems in performing either of the MVF tasks and showed high compliance with both MVF devices. We did not find significant differences in the assessed items between the conditions (vividness: $t_{19} = 0.18$, $p = .86$; intensity: $t_{19} = 0.2$, $p = 0.84$). The mean values of the ratings for the items used in both conditions were between 4.95 and 5.8 (Table 1).

Table 1. Ratings on the intensity and vividness of mirror illusions for the mirror box and mirror glasses conditions.

Mirror illusion item	Mirror glasses	Mirror box	t (19)	p
Intensity (*M+SD*)	5.8 (± 1.44)	5.75 (± 1.68)	0.2	0.84
Vividness (*M+SD*)	5.3 (± 1.59)	4.95 (± 2.11)	0.18	0.86

Results are reported with Mean ± Standard Deviation of the Mean (*M ± SD*). Comparisons of the two items between conditions were conducted with paired sample t-tests with Bonferroni adjusted alpha-values of 0.025 (0.05/2). Numerical rating scale ranging from 1 ('as clear and vivid as a real perceptual experience') to 7 ('not at all clear and vivid').

Functional Imaging Data

Task-related brain activation in both MVF conditions

Imaging data revealed significant fMRI activations in the left sensorimotor cortex corresponding to the moving right hand in both MVF conditions (MNI coordinates: MB x=-40, y=-22, z=56, Z=7.0; MG x=-38, y=-24, z=60, Z=7.26). Additionally, a significant cluster of activation was found in the right sensorimotor cortex representing the non-mirrored left hand in both MVF conditions (MB x=40, y=-36, z=52, Z=3.64; MG x=42, y=-12, z=62, Z=4.99) (Table 2, Fig. 2). Furthermore, significant clusters of activation were found in the supplementary motor area (SMA), the premotor cortex (PMC), the ipsilateral cerebellum and the secondary somatosensory cortex (SII). Besides these sensorimotor activations, we found additional peak voxels in the primary auditory cortex (Heschl's gyrus) and visual areas like the lateral occipital cortex (LOC) (Table 2, Fig. 2).

The direct comparisons between both MVF conditions (MG > MB and MG < MB) yielded no significant differences in whole-brain activations, indicating comparable patterns of fMRI activations for both MVF tasks.

28
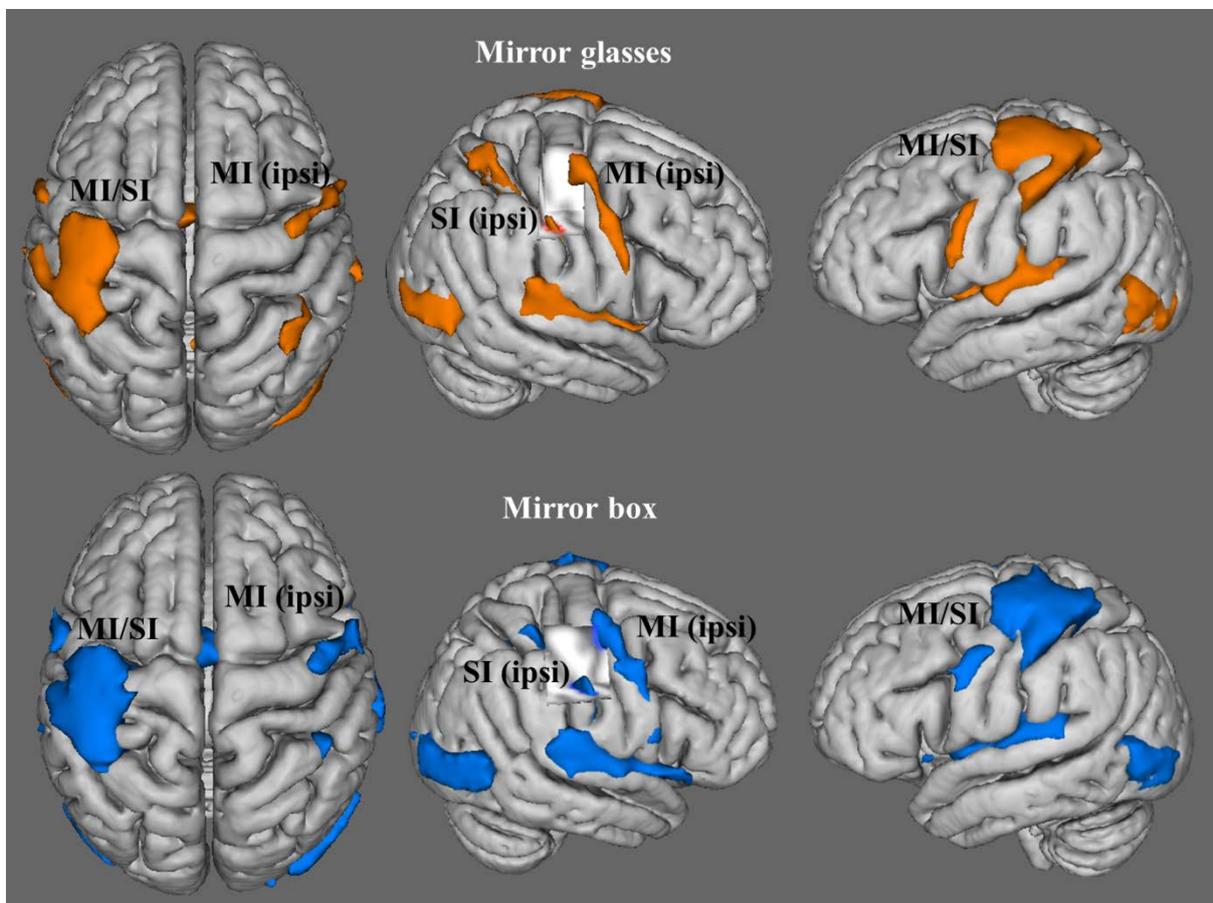
Fig. 2. Task-related brain activation for the mirror glasses and mirror box conditions. fMRI activations were mapped on a FSL render image. MI/SI = primary motor/somatosensory cortex, ipsi = ipsilateral to the executing (right) hand.

Task-dependent functional connectivity between hand areas during both MVF conditions

In order to test whether the motor representation of the actually moving hand (MI_{contra}) was functionally coupled with MI_{ipsi} of the non-mirrored (hidden) hand, we used a PPI analysis with a seed region in MI_{contra}. We found a significant positive psychophysiological interaction between MI_{contra} with the sensorimotor representation of the non-mirrored hand (x=40, y=-24, z=66, Z=3.91) in the MG condition (Table 3, Fig. 3). No significant positive correlation was found between MI_{contra} and the sensorimotor representation of the non-mirrored hand in the MB condition. In both MVF conditions, MI_{contra} showed significant positive functional connectivity with frontal lobe regions (middle and superior frontal gyrus) and the LOC. Furthermore, in both MVF conditions significant positive psychophysiological interactions were found with the precentral gyrus. However, these peak voxels were located too medially to be a correlate of the mirrored right hand (MB x=2, y=-26, z=78; MG x=6, y=-28, z=76) (Table 3, Fig. 3). In the MB condition we found further positive psychophysiological interactions with the SMA. In the MG condition we found additionally significant task-related functional connectivity with the middle and superior frontal gyrus, the paracingulate gyrus, the angular gyrus and the posterior cingulate gyrus (Table 3, Fig. 3).

We also tested for significant negative psychophysiological interactions (decouplings). We did not find significant decouplings between the representations of both hands in the predefined ROIs in either of the MVF conditions. For an overview about significant negative psychophysiological interactions other than those in the specified ROIs see S1 Table.

Table 2. Brain regions and peak voxel coordinates showing significant task-related brain activation for the mirror box and mirror glasses conditions.

Region: left hemisphere, contralateral to the moving hand	MNI-coordinates			z-score	extent [voxels]	Region: right hemisphere, ipsilateral to the moving hand	MNI-coordinates			z-score	extent [voxels]
	x	y	z				x	y	z		
Mirror glasses											
Precentral gyrus	-60	6	30	4.53	148	Precentral gyrus	56	0	52	5.48	838
Precentral gyrus	-34	-22	70	6.47	5362	Precentral gyrus	42	-12	62	4.99	838
Postcentral gyrus	-38	-24	60	7.26	5362	Postcentral gyrus	54	-18	40	4.24	107
Postcentral gyrus	-42	-26	50	6.71	5362	Superior parietal lobule	38	-48	70	4.13	351
Supplementary motor area	-4	-6	58	4.89	258	Planum temporale	60	-16	8	5.94	1547
Putamen	-26	-8	12	4.33	146	Cerebellum	8	-56	-10	5.9	115
Lateral occipital cortex	-44	-76	4	5.79	1988	Lateral occipital cortex	50	-64	6	6.02	1548
						Lateral occipital cortex	30	-78	32	4.31	115
Mirror box											
Precentral gyrus	-62	2	32	4.6	204	Postcentral gyrus	40	-36	52	3.64	92

Precentral gyrus	-40	-22	56	7	5967	Secondary somatosensory cortex	66	-20	18	6.43	3515
Postcentral gyrus	-38	-24	62	6.97	5967	Cerebellum	8	-58	-10	5.54	109
Heschl's gyrus	-50	-20	8	7.08	5967	Lateral occipital cortex	48	-68	-2	6.41	1701
Supplementary motor area	-4	-4	60	5.7	445	Occipital pole	16	-96	-8	3.98	97
Thalamus	-14	-20	2	5.4	109						
Lateral occipital cortex	-48	-76	6	5.1	1827						
Occipital fusiform gyrus	-18	-80	-10	4.3	181						

Areas of significant fMRI response were determined using clusters identified by a $z > 3.0$ threshold and a corrected cluster threshold of $p = 0.05$ assuming a Gaussian random field for the z-statistics. Coordinates are displayed in the Montreal Neurological Institute (MNI152) space.

Table 3. Brain regions showing significant positive psychophysiological interactions (PPI) with the motor representation of the moving hand for the mirror box and mirror glasses conditions.

Region: left hemisphere, contralateral to the moving hand	MNI-coordinates			z-score	extent [voxels]	Region: right hemisphere, ipsilateral to the moving hand	MNI-coordinates			z-score	extent [voxels]
	x	y	z				x	y	z		
Mirror glasses											
Superior frontal gyrus	-22	30	46	4.81	671	Precentral gyrus	6	-28	76	4.05	249
Middle frontal gyrus	-38	10	50	4.16	156	Postcentral gyrus	40	-24	66	3.91	95
Posterior cingulate gyrus	-10	-44	34	4.01	246	Paracingulate gyrus	2	40	-12	4.14	200
Angular gyrus	-46	-56	30	3.94	135						
Lateral occipital cortex	-34	-74	42	3.93	203						
Mirror box											
Precentral gyrus	-28	-26	74	3.86	77	Precentral gyrus	2	-26	78	3.79	172
Middle frontal gyrus	-26	32	46	3.84	282						
Supplementary motor area	-2	-2	74	3.66	78						

| Lateral occipital cortex | -40 | -70 | 34 | 3.86 | 111 | |

Seed regions of interests derived from subject specific peak voxels in the primary motor cortex of the single contrasts mirror glasses and mirror box. PPIs were calculated based on deconvolved fMRI signals from individual seed voxels obtained with a radial sphere of 5 mm. Areas of significant fMRI-responses were determined using clusters identified by a $z > 3.0$ threshold and a corrected cluster threshold of $p = 0.05$ assuming a Gaussian random field for the z-statistics. Coordinates are displayed in the Montreal Neurological Institute (MNI152) space
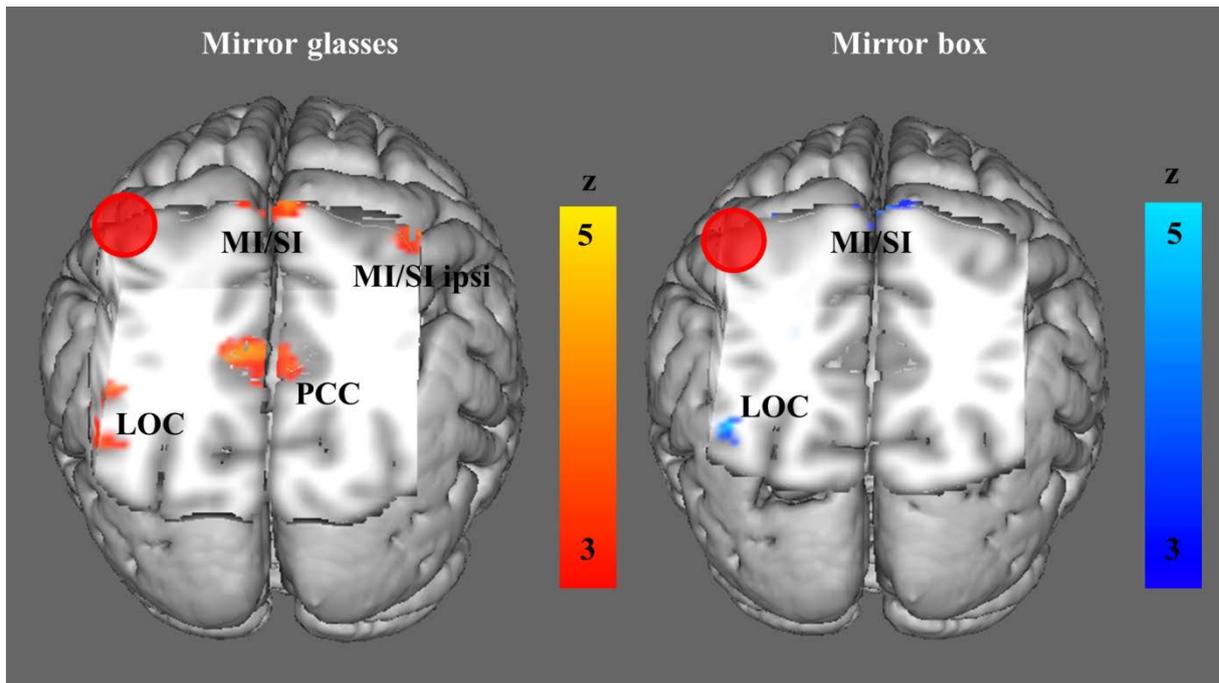
Fig. 3. Brain regions showing significant positive psychophysiological interactions (PPI) with the motor representation of the moving hand. fMRI activations were mapped on a FSL render image. For illustrative purposes the spherical seed region of interest in the left primary motor cortex is also shown as red-colored sphere. MI/SI = primary motor/somatosensory cortex, LOC = lateral occipital cortex, PCC = posterior cingulate cortex, ipsi = ipsilateral to the executing (right) hand.

Discussion

The present study evaluated the utility of MG by comparing it with the MB and yielded three important results: (1) We did not find significant differences in subjective ratings capturing mirror illusion capacity between either MVF intervention, indicating similar capabilities of both to induce mirror illusions. (2) We found similar patterns of task-related brain activation for both conditions, including the sensorimotor representation of the non-mirrored hand as well as other brain areas typically found in MVF tasks (Deconinck et al., 2014; Matthys et al., 2009). Critically, the direct comparison of both MVF interventions yielded no significant differences in fMRI activation. (3) Furthermore, we found increased interhemispheric connectivity between both hand representations only in the MG condition. This suggests that the motor representation of the non-mirrored hand in the MG condition is modulated via this interhemispheric connection. Due to the fact that the hand region in MI$_{ipsi}$ was activated in both MVF conditions we assume that the MB condition works by a different neural mechanism.

Comparable subjective quality of mirror illusions

To our knowledge this is the first study quantifying the subjective quality of MG in comparison to the well-established MB. The MG have been discussed to be superior to the classical MB and even virtual-reality applications of the MB because they provide a naturalistic view on the reflection of the actually moving limb without seeing the mirrored limb additionally which potentially has a distracting effect (Hadoush et al., 2013; Tsakiris, Schuetz-Bosbach, et al., 2007; Walsh & Bannister, 2010). Neither the vividness nor the intensity of mirror illusions differed significantly between both mirror tasks. The most notable difference between both MVF conditions was the presentation of only the visual reflection of the moving right hand in the MG compared with both hands appearing to move in synchrony in the MB condition. We hypothesized to find higher subjective ratings on mirror illusions in the MG condition, because it has been proposed that seeing the moving hand in addition to the visual reflection might interfere with mirror illusions and the accompanying recruitment of the sensorimotor representation of the hidden hand (Hadoush et al., 2013; Walsh & Bannister, 2010). Despite of the low to medium high ratings for the mirror illusion items used, the subjective ratings were comparable to other studies using these items (Diers et al., 2015, 2010) including patient studies demonstrating a therapeutic effect of MVF (Foell et al., 2014). It is important to note that we did not instruct the participants to perform motor imagery during the MVF task. We used the standard (original) instruction for clinical studies as has been used, for example, by Ramachandran & Rogers-Ramachandran (Ramachandran, Rogers-Ramachandran & Cobb, 1995), who originally reported the effects of mirror training on phantom pain. It has been shown that mirror illusions and the concomitant recruitment of the affected limb representation can be improved by combining MVF with motor imagery (Fukumura, Sugawara, Tanabe, Ushiba, & Tomita, 2007; McCabe et al., 2008). Thus, we assume that the moderate levels of induced mirror illusions can be increased when MVF is combined with motor imagery.

Comparable task-related brain activation

We found comparable patterns of functional brain activation between both MVF conditions, including those areas that have been shown to be typically activated in a motor MVF task (Deconinck et al., 2014; Matthys et al., 2009). In contrast to our hypothesis, we did not find significant differences in fMRI activations in the MI$_{ipsi}$ corresponding to the hidden left hand or in any other brain region between both MVF tasks (Hadoush et al., 2013).

The visual illusion of the moving hand has been discussed to be the experimental substrate of MVF-related excitation of the MI corresponding to the non-mirrored hand (Hadoush et al., 2013). In both MVF conditions, we found extended fMRI activations in the right sensorimotor cortex, corresponding to the non-mirrored (hidden) hand, in addition to a significant activation of the sensorimotor representation of the actually moving hand. A recruitment of the sensorimotor representation ipsilateral to the moving hand during a MB task was also found in former fMRI studies using MVF (Diers et al., 2015, 2010; Shinoura et al., 2008) and has been reported to be a stable neural correlate in a recent meta-analysis including 33 MVF studies (Deconinck et al., 2014). It has been shown that ipsilateral hand movement (Liepert, Dettmers, Terborg, & Weiller, 2001; Muellbacher et al., 2002) as well as passive observation of contralateral limb movements can induce excitability changes in MI$_{ipsi}$ (Maeda et al., 2014; Strafella & Paus, 2000). The interaction between ipsilateral motor observation (as realized in a MB task) and contralateral motor execution has been discussed to drive the excitability changes in MI$_{ipsi}$ during MVF (Garry, Loftus, & Summers, 2005). Garry et al. (2005) were able to show that the motor observation component alone increases excitability in MI$_{ipsi}$, whereby facilitation of MI$_{ipsi}$ excitability was strongest with the mirror reflection. Moreover, Diers et al. (2010) found increased fMRI activation in MI$_{ipsi}$ in a group of healthy controls and amputees without phantom limb pain in a motor execution as well as a MVF task, but activity was higher with MVF, which suggest an additional effect of the motor observation component for the recruitment of the hand representation corresponding to the hand seen in the mirror. We did not include a pure motor execution condition in this study, but we can conclude from results of previous studies that activations would be located in similar regions, although less prominent (Diers et al., 2010; Lotze, Montoya, et al., 1999; Lotze et al., 2001).

In a magnetoencephalographic study, Hadoush et al. (2013) investigated the effects of seeing the physically moving hand in addition to the mirror reflection of the moving hand on MI$_{ipsi}$ excitability within a classical MB setup. The subjects were tested in a within-subjects design performing a MB task with either their actually moving hand out of view or visible. Hadoush et al. (2013) reported a higher capability to recruit MI$_{ipsi}$ and a clearer visual illusion when the executing hand was out of view. We also hypothesized to find a stronger recruitment of MI$_{ipsi}$ in the MG condition because subjects can more easily focus on the mirror illusion (Walsh & Bannister, 2010). Although we did not use an additional item to specifically assess the potentially distracting effect of seeing the executing hand on mirror illusions in the MB condition (Hadoush et al., 2013), we found no significant differences in the capability to recruit the MI$_{ipsi}$ between the two MVF conditions as revealed by the direct comparison between them. In contrast to Hadoush et al. (2013), we did not instruct the subjects to perform motor imagery during the MVF task. It has been discussed that mirror illusions and the concomitant recruitment of the affected limb representation can be improved by combining MVF with motor imagery (Deconinck et al., 2014; Fukumura et al., 2007; McCabe et al., 2008) and possibly the additional effect of motor imagery might differ between the MB and MG condition by seeing just one compared with two hand moving in synchrony. Thus, the proposed beneficial effect on MI$_{ipsi}$ recruitment caused by disabling the vision of the actually moving limb compared with seeing both hands moving in synchrony cannot be supported by our findings.

Moreover, we found additional fMRI activations during the mirror tasks in PMC, the ipsilateral cerebellum, SMA, the thalamus, the LOC as well as SII, which constitute brain regions typically activated in hand motor tasks like the MB task (Deconinck et al., 2014; Matthys et al., 2009). Clusters of activation were further found in the primary auditory cortex, which were expected due to the auditory pacing signal present during the movement trials in both mirror tasks.

Despite the differences in the amount of visual input between both MVF conditions by seeing just one hand in the MG compared with two hands appearing to move in synchrony in the MB, neither the single condition contrasts nor the direct comparison between both MVF conditions revealed significant differences in visual areas. In both MVF conditions clusters of activation in the LOC showed similar cluster extensions and peak maxima between both hemispheres.

Different patterns of task-dependent functional connectivity

It has been proposed that the MVF related recruitment of the affected motor limb representation (MI_{ipsi}) is due to contralateral projections arising from the motor representation of the moving (intact) limb (MI_{contra}) (Ezendam, Bongers, & Jannink, 2009; Foell et al., 2014; Hamzei et al., 2012). To specifically address this hypothesis of an MVF-related increase in interhemispheric connectivity between both motor hand representations, we applied PPI analysis with individually defined ROIs in the MI_{contra} (Deconinck et al., 2014). So far there is a lack of studies on functional connectivity between brain areas to reveal the neural mechanisms underlying MFV (Deconinck et al., 2014).

We found a significant increase in interhemispheric connectivity between MI_{contra} and the sensorimotor representation of the non-mirrored hand in the MG condition, but not in the MB condition. The absence of significant interhemispheric communication in the MB condition is in line with the finding of a recent MVF study examining motor improvement in the limb seen in the mirror in two patients with callosal disconnection (Nojima et al., 2013). These callosal patients showed improved motor function in the untrained hand seen in the mirror after mirror training, which cannot be explained by intermanual transfer mediated by transcallosal fibers in these subjects. Moreover, Hamzei et al. (2012) found increased functional and effective connectivity between various brain regions, but not between both motor hand areas in a group of healthy volunteers performing mirror training. Thus, the recruitment of the sensorimotor representation corresponding to the non-mirrored hand was likely not mediated by interhemispheric communication via transcallosal fibers between the hand areas in the MB condition.

We found a significant increase in task-related interhemispheric connectivity only in the MG condition. However, in both MFV conditions the ipsilateral sensorimotor representation of the non-mirrored hand was significantly activated and fMRI activity did not differ between both MVF conditions as revealed by the direct comparison between both MVF conditions. Thus, our findings indicate that the mechanism, by which the ipsilateral sensorimotor representation of the non-mirrored hand was recruited, might vary between both MVF conditions. Whereas interhemispheric communication seems to be important for the recruitment of MI_{ipsi} in the MG condition, it might just play a minor role in the MB condition. How can this difference

in the recruitment of the sensorimotor representation of the non-mirrored hand be explained?

Our ROI was located in the motor representation of the moving hand, in order to specifically address the hypothesis of increased interhemispheric communication mediating the recruitment of MI_{ipsi}. Thus, we can only speculate which alternative mechanism might account for the recruitment of sensorimotor representation of the hidden hand in the MB. It has already been proposed that afferent information from the visual cortex might re-establish coherence in the limb representation in MI_{ipsi} by recruiting the preserved motor representation in patient groups (Giraux & Sirigu, 2003). In both MVF conditions we found increased psychophysiological interactions between the LOC and MI_{contra}, indicating that afferent input from visual areas might be an attractive candidate for the recruitment of the sensorimotor representation of the non-mirrored hand.

Study limitations

A limitation of the current study is that we only looked at the instant neuromodulatory effects of MVF. Thus, we cannot exclude the possibility of use-dependent dynamics in functional brain activity by long-term training with our MVF devices (Deconinck et al., 2014; Hamzei et al., 2012).

Furthermore, it has to be considered that healthy subjects performed both mirror tasks. In future studies, the MG will have to be evaluated in specific patient groups such as patients with specific motor deficits or chronic pain.

A further limitation of this study is that we did not apply measures of effective connectivity (e.g., dynamic causal modelling or Granger causality) because our experimental design was not factorial and therefore is not suitable for applying effective connectivity analysis (Friston, Moran, & Seth, 2013; Stephan & Friston, 2010). As highlighted in the original publication on dynamic causal modelling by Friston et al. (2003) a multi-factorial design with one factor assumed to be a driving input (e.g., sensory stimulation) and another factor acting as modulatory input (e.g., attention) is suggested.

Conclusions

Based on comparable patterns of brain activation and subjective ratings on mirror illusions, we conclude that MG might be a versatile substitute of the MB in the treatment of chronic pain as well as the functional recovery in different patient groups. Compared with the MB, MG might be favoured due to their higher manageability in everyday therapy and research.

Moreover, we found evidence that the recruitment of the hand representation of the non-mirrored hand might be mediated by interhemispheric communication in the MG, but not in the MB condition, indicating that different neural mechanisms might contribute to the recruitment of the cortical hand representation of the non-mirrored hand in the MB versus MG condition. This difference might be explained by the conceptual difference of seeing both hands moving in synchrony (MB) versus seeing only the visual reflection of the moving hand (MG).

Acknowledgement

References

Altschuler, E. L., & Hu, J. (2008). Mirror therapy in a patient with a fractured wrist and no active wrist extension. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery,* 42(2), 110–111. doi:10.1080/02844310701510355

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007). Non-linear registration aka Spatial normalization. *FMRIB Technical Report* TR07JA2, (June).

Chan, B. L., Witt, R., Charrow, A. P., Magee, A., Howard, R., Pasquina, P. F., … Tsao, J. W. (2007). Mirror therapy for phantom limb pain. *New England Journal of Medicine*, 357(21), 2206–2207. doi:10.1056/NEJMc071927

Deconinck, F., Smorenburg, A. R. P., Benham, A., Ledebt, A., Feltham, M. G., & Savelsbergh, G. J. P. (2014). Reflections on Mirror Therapy: A Systematic Review of the Effect of Mirror Visual Feedback on the Brain. *Neurorehabilitation and Neural Repair*, 29(4), 349–361. doi:10.1177/1545968314546134

Diers, M., Christmann, C., Koeppe, C., Ruf, M., & Flor, H. (2010). Mirrored, imagined and executed movements differentially activate sensorimotor cortex in amputees with and without phantom limb pain. *Pain*, 149(2), 296–304. doi:10.1016/j.pain.2010.02.020

Diers, M., Kamping, S., Kirsch, P., Rance, M., Bekrater-Bodmann, R., Foell, J., … Flor, H. (2015). Illusion-related brain activations: A new virtual reality mirror box system for use during functional magnetic resonance imaging. *Brain Research*, 1594, 173–182. doi:10.1016/j.brainres.2014.11.001.

Eickhoff, S. B., Paus, T., Caspers, S., Grosbras, M. H., Evans, A. C., Zilles, K., & Amunts, K. (2007). Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. *NeuroImage*, 36, 511–521. doi:10.1016/j.neuroimage.2007.03.060

Ezendam, D., Bongers, R. M., & Jannink, M. J. (2009). Systematic review of the effectiveness of mirror therapy in upper extremity function. *Disability and Rehabilitation*, 31(26), 2135–49. doi:10.3109/09638280902887768

Foell, J., Bekrater-Bodmann, R., Diers, M., & Flor, H. (2014). Mirror therapy for phantom limb pain: Brain changes and the role of body representation.

European Journal of Pain (London, England), 18(5), 1–11. doi:10.1002/j.1532-2149.2013.00433.x

Fotopoulou, A., Jenkinson, P. M., Tsakiris, M., Haggard, P., Rudd, A., & Kopelman, M. D. (2011). Mirror-view reverses somatoparaphrenia: Dissociation between first- and third-person perspectives on body ownership. *Neuropsychologia*, 49(14), 3946–3955. doi:10.1016/j.neuropsychologia.2011.10.011

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage*, 66(3), 218-29. doi:10.1006/nimg.1997.0291

Friston, K. J., Harrison, L., & Penny, W. (2003). Dynamic causal modelling. *NeuroImage,* 19(4), 1273-302. doi:10.1016/S1053-8119(03)00202-7

Friston, K. J., Moran, R., & Seth, A. K. (2013). Analysing connectivity with Granger causality and dynamic causal modelling. *Current Opinion in Neurobiology*, 23(2), doi:172–178. 10.1016/j.conb.2012.11.010

Fukumura, K., Sugawara, K., Tanabe, S., Ushiba, J., & Tomita, Y. (2007). Influence of mirror therapy on human motor cortex. *The International Journal of Neuroscience,* 117(7), 1039-1048. doi:10.1080/00207450600936841

Garry, M. I., Loftus, A., & Summers, J. J. (2005). Mirror, mirror on the wall: viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability. *Experimental Brain Research*, 163(1), 118–22. doi:10.1007/s00221-005-2226-9

Giraux, P., & Sirigu, A. (2003). Illusory movements of the paralyzed limb restore motor cortex activity. *NeuroImage*, 20(Suppl1), 107–111. doi:10.1016/j.neuroimage.2003.09.024

Hadoush, H., Mano, H., Sunagawa, T., Nakanishi, K., & Ochi, M. (2013). Optimization of mirror therapy to excite ipsilateral primary motor cortex. NeuroRehabilitation, 32(3), 617–24. doi:10.3233/NRE-130884

Hamzei, F., Läppchen, C. H., Glauche, V., Mader, I., Rijntjes, M., & Weiller, C. (2012) Functional plasticity induced by mirror training: the mirror as the element connecting both hands to one hemisphere. *Neurorehabilitation and Neural Repair*, 26(5), 484–96. doi:10.1177/1545968311427917.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*, 17(2), 825–841. doi:10.1006/nimg.2002.1132

Läppchen, C. H., Ringer, T., Blessin, J., Seidel, G., Grieshammer, S., Lange, R., & Hamzei, F. (2012). Optical illusion alters M1 excitability after mirror therapy: a TMS study. *Journal of Neurophysiology*, 108(10), 2857–61. doi:10.1152/jn.00321.2012

Liepert, J., Dettmers, C., Terborg, C., & Weiller, C. (2001). Inhibition of ipsilateral motor cortex during phasic generation of low force. *Clinical Neurophysiology*, 112(1), 114–121. doi:10.1016/S1388-2457(00)00503-4

Lotze, M., Montoya, P., Erb, M., Hulsmann, E., Flor, H., Klose, U., ... Grodd, W. (1999). Activation of cortical and cerebellar motor areas during executed and imagined hand movements: An fMRI study. *Journal of Cognitive Neuroscience,* 11(5), 491–501. doi:10.1162/089892999563553

Lotze, M., Flor, H., Grodd, W., Larbig, W., & Birbaumer, N. (2001). Phantom movements and pain. An fMRI study in upper limb amputees. *Brain*, 124(Pt 11), 2268–77. doi:10.1093/brain/124.11.2268

Maeda, F., Kleiner-Fisman, G., Pascual-Leone, A., Rogasch, N. C., Daskalakis, Z. J., Fitzgerald, P. B., … Rozzi, S. (2014). Motor Facilitation While Observing Hand Actions. *Journal of Neurophysiology,* 87(3), 1329–1335. doi:0.1152/jn.00773.2000

Matthys, K., Smits, M., Van der Geest, J. N., Van der Lugt, A., Seurinck, R., Stam, H. J., & Selles, R. W. (2009). Mirror-induced visual illusion of hand movements: a functional magnetic resonance imaging study. *Archives of Physical Medicine and Rehabilitation*, 90(4), 675–81. doi:10.1016/j.apmr.2008.09.571

McCabe, C. S. (2003). A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). *Rheumatology,* 42(1), 97–101. doi:10.1093/rheumatology/keg041

McCabe, C., Haigh, R. C., & Blake, D. R. (2008). Mirror visual feedback for the treatment of complex regional pain syndrome (type 1). *Current Pain and Headache Reports*, 12(2), 103–107. doi:10.1007/s11916-008-0020-7

Michielsen, M. E., Selles, R. W., van der Geest, J. N., Eckhardt, M., Yavuzer, G., Stam, H. J., ... Bussmann, J. B. J. (2011). Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. *Neurorehabilitation and Neural Repair,* 25(3), 223–33. doi:10.1177/1545968310385127

Moseley, G. L., Gallace A., & Spence, C. (2008). Is mirror therapy all it is cracked up to be? Current evidence and future directions. *Pain*, 138(1), doi:7–10. 10.1016/j.pain.2008.06.026

Muellbacher, W., Ziemann, U., Wissel, J., Dang, N., Kofler, M., Facchini, S., … Hallet, M. (2002). Early consolidation in human primary motor cortex. *Nature*, 415(6827), 640–644. doi:10.1038/nature712

Nojima, I., Mima, T., Koganemaru, S., Thabit, M. N., Fukuyama, H., & Kawamata, T. (2012). Human Motor Plasticity Induced by Mirror Visual Feedback. *Journal of Neuroscience*, 32(4), 1293–1300. doi:10.1523/JNEUROSCI.5364-11.2012

Nojima, I., Oga, T., Fukuyama, H., Kawamata, T., & Mima, T. (2013). Mirror visual feedback can induce motor learning in patients with callosal disconnection. *Experimental Brain Research*, 1–5. doi:10.1007/s00221-013-3486-4

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. doi: 10.1016/0028-3932(71)90067-4

O'Reilly, J. X., Woolrich, M. W., Behrens, T. E. J., Smith, S. M., & Johansen-Berg, H. (2012). Tools of the Trade: Psychophysiological Interactions and Functional Connectivity. *Social Cognitive and Affective Neuroscience,* 7(5), 604–609. doi:10.1093/scan/nss055

Ramachandran, V., Stewart, M., & Rogers-Ramachandran, D. (1992). Perceptual Correlates of Massive Cortical Reorganization. *Neuroreport*, 3(7), 583–586. doi:10.1097/00001756-199207000-00009

Ramachandran, V. S., Rogers-Ramachandran, D., & Cobb, S. (1995). Touching the phantom limb. *Nature,* 377(6549), 489–490. doi:10.1038/377489a0

Ramachandran, V., & Rogers-Ramachandran, D. (1996). Synaesthesia in phantom limbs induced with mirrors. *Proceedings Biological Sciences*, 263(1369), 377–86. doi:10.1098/rspb.1996.0058

Sathian K., Greenspan, A. I., & Wolf, S. L. (2000). Doing It with Mirrors: A Case Study of a Novel Approach to Neurorehabilitation. *Neurorehabilitation and Neural Repair,* 14(3), 73–76. doi:10.1177/1545968308327625

Sheehan, P. W. (1967). A shortened form of Betts' questionnaire upon mental imagery. *Journal of Clinical Psychology*, 23(3), 386–389. doi:10.1002/1097-4679(196707)23

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–55. doi:10.1002/hbm.10062

Shinoura, N., Suzuki, Y., Watanabe, Y., Yamada, R., Tabei, Y., Saito, K., ... Yagi, K. (2008). Mirror therapy activates outside of cerebellum and ipsilateral M1. *NeuroRehabilitation*, 23(3), 245–52.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23 Suppl 1*, 208–219. doi:10.1016/j.neuroimage.2004.07.051

Stephan, K. E., & Friston, K. J. (2010). Analyzing effective connectivity with fMRI. Wiley Interdisciplinary Reviews. *Cognitive Science,* 1(3), 446–459. doi:10.1002/wcs.58

Strafella, A. P., & Paus, T. (2000). Modulation of cortical excitability during action observation : a transcranial magnetic stimulation study. *NeuroReport,* 11(10), 2289–2292. http://dx.doi.org/10.1097/00001756-200007140-00044

Sütbeyaz, S., Yavuzer, G., Sezer, N., & Koseoglu, B. F. (2007). Mirror Therapy Enhances Lower-Extremity Motor Recovery and Motor Functioning After Stroke: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation,* 88(5), 555–559. doi:10.1016/j.apmr.2007.02.034

Tsakiris, M., Schuetz-Bosbach, S., & Gallagher, S. (2007). On agency and body-ownership: Phenomenological and neurocognitive reflections. *Consciousness and Cognition*, 16(3), 645–660. doi:10.1016/j.concog.2007.05.012

Walsh, G., & Bannister, J. (2010). A device for the relief of phantom limb pain and rehabilitation in stroke. *Optometry and Vision Science* , 87(12), E971-8. doi:10.1097/OPX.0b013e3181fcabc3

Woolrich, M. W., Behrens, T. E. J., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for FMRI group analysis using Bayesian inference. *NeuroImage*, 21(Suppl 1), 1732–47. doi:10.1016/j.neuroimage.2004.07.051

Yavuzer, G., Selles, R., Sezer, N., Sütbeyaz, S., Bussmann, J. B., Köseoğlu, F., ... Yagi, K. (2008). Mirror Therapy Improves Hand Function in Subacute Stroke: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation*, 89(3), 393–398. doi:10.1016/j.apmr.2007.08.162

Supporting Information

S1 Table. Brain regions revealing significant negative psychophysiological interactions (PPI) with the motor representation of the moving hand for the mirror box and mirror glasses conditions.

Region: left hemisphere (contralateral to the moving hand)	MNI-coordinates			z-score	extent [voxels]	Region: right hemisphere (ipsilateral to the moving hand)	MNI-coordinates			z-score	extent [voxels]
	x	y	z				x	y	z		
Mirror glasses											
Secondary somatosensory cortex	-56	-38	22	4.89	2143	Inferior frontal gyrus	48	10	18	3.92	90
Thalamus	-8	-16	4	3.92	73	Anterior cingulate cortex	6	12	38	4.24	152
						Central opercular cortex	44	8	2	4.57	1026
						Posterior cingulate cortex	8	-26	44	4.07	71
						Supramarginal gyrus	60	-40	18	5.24	1175
Mirror box											
Anterior cingulate cortex	-8	10	38	4.19	305	Insular cortex	40	10	-4	4.71	1195
Insular cortex	-34	22	-2	4.85	1154	Superior temporal gyrus	62	-36	10	4.77	1681
Planum temporale	-52	-24	4	4.36	905						

Areas of significant fMRI-responses were determined using clusters identified by a $z > 3.0$ threshold and a corrected cluster threshold of $p = 0.05$ assuming a Gaussian random field for the z-statistics. Coordinates are displayed in the Montreal Neurological Institute (MNI152) space.

Study 2

Evoked phantom sensations in amputees: a link between neural processing of body illusions and altered body perception[2]

---

[2] Milde, C., Diers, M., Andoh, J., Becker, S., Fuchs, X., Trojan, J., Bekrater-Bodmann, R., & Flor, H. (2017). *Evoked phantom sensations in amputees: a link between neural processing of body illusions and altered body perception.* Manuscript in preparation.

Abstract

A disturbed body perception is characteristic for various neurological and mental disorders and becomes particularly evident in phantom phenomena after limb amputation. Most amputees continue to perceive the amputated limb and some perceive sensations in their missing limb, when body parts adjacent to or remote from the amputated limb are stimulated (evoked phantom sensations). We examined the neural correlates of evoked phantom sensations and hypothesized that they can be linked to neural networks underlying body illusions such as illusions inducing the percept of having a third arm. Using functional MRI, we investigated 12 upper-limb amputees who reliably perceived non-painful evoked phantom sensations and 12 yoked controls. We used non-painful electrical and tactile stimulation to elicit non-painful phantom sensations and also stimulated at control sites that did not elicit phantom sensations. All sites were remote from the amputation site to avoid interference of local amputation-induced changes. In the controls, we stimulated at anatomically matched body sites.

Using a conjunction analysis, we found increased brain activation in the left ventral frontal (BA44/45) and premotor cortices as well as in the insula and putamen during the elicitation of phantom sensations compared to both control conditions (within-amputees and yoked controls). Moreover, the comparison between the evoked phantom sensation and control condition in amputees showed significant activation in inferior and intraparietal regions and the secondary somatosensory cortex. Regressive generalized psychophysiological interaction analyses further revealed a widespread network showing significant positive intra-parietal and fronto-parietal connectivity. This network comprised the left ventral frontal and premotor cortices that interacted with activation in the superior parietal lobe. The present findings associate non-painful phantom sensations with a fronto-parietal network similar to that reported in body illusions and altered body perception. These data emphasize the role of crossmodal stimulation in normalizing dysfunctional body representations.

Introduction

The perception of one's body can substantially differ from its physical appearance if there is a mismatch between the sensory modalities or as a consequence of brain damage (Tsakiris, 2010; Blanke *et al.*, 2015). This becomes particularly evident in the case of amputation where patients frequently report phantom phenomena, i.e., the continued presence of the amputated limb or perceptions that are allocated to the missing limb. The phantom limb is often felt in a distorted or cramped position (Jensen, Krebs, Nielsen, & Rasmussen, 1984; Jensen et al., 1985) and about 60-80% of the amputees report phantom pain, a painful sensation perceived in the amputated limb (Jensen *et al.*, 1983; Hanley *et al.*, 2009). Non-painful phantom phenomena are phenomenologically heterogeneous – while phantom sensations are described as a specific somatic sensation such as tingling, warmth, cold, itch or movement noticed in the phantom limb, phantom limb awareness is defined as are more general knowledge of the existence/presence of the missing limb as one's own (Hunter *et al.* 2003). Phantom phenomena can be spontaneous or related to external stimulation applied to specific body parts, the latter being termed 'evoked phantom sensation' (Cronholm, 1951). Evoked phantom sensations can have a specific somatic quality or be described as a change in the general awareness of the presence of the phantom limb (Hunter *et al.* 2003).

The neural mechanisms underlying painful and non-painful phantom sensations such as evoked phantom sensations are under investigation. Based on findings of massive reorganization in SI following dorsal rhizotomies in macaques (Pons *et al.*, 1991), Ramachandran *et al.* (1992) proposed that both painful and non-painful phantom phenomena might be a consequence of SI reorganization. They observed that stimulation applied to the face, which is represented adjacent to the upper limb in SI, elicited sensations in the phantom limb showing a one-to-one topographical correspondence between stimulation sites on the face and the phantom. Subsequent studies however, indicated that reorganization in SI is related to painful but not non-painful phantom phenomena (Flor *et al.*, 1995; Grüsser *et al.*, 2001). These studies found a high correlation between phantom pain and SI reorganization, but no such relationship for non-painful phantom phenomena, including evoked phantom sensations. Moreover, evoked phantom sensations have often been reported to be elicited at body sites represented remote from or contralateral to the SI

representation of the amputated limb (Knecht *et al.*, 1998; Grüsser *et al.*, 2004; Giummarra *et al.*, 2011; Andoh *et al.*, 2017), questioning dysfunctional changes in SI topography. Grüsser *et al.* (2004) investigated two upper limb amputees in whom phantom sensations could be evoked at remote body sites at the ipsi- and contralateral leg. The authors found a medial shift of the mouth representation, however, no reorganization in the representation of the feet. Based on their findings, Grüsser *et al.* (2004) discussed the role of the posterior parietal regions and the secondary somatosensory cortex, which reveals a greater reorganizational potential than SI, for non-painful phantom sensations.

The rubber hand illusion resembles the perception of non-painful phantoms. In the rubber hand illusion synchronous stroking of a visible artificial and the participant's hidden hand induces a *referral of touch* from the actual to the artificial rubber hand and to the experience of ownership for the artificial limb (Botvinick & Cohen, 1998). Increased activation in ventral frontal (i.e., premotor cortex and BA44/45) and posterior parietal (i.e., the intraparietal sulci) have been shown to be related with the rubber hand illusion (Ehrsson *et al.*, 2004, 2005). These findings suggest that non-painful phantom phenomena might be also related to brain activation in ventral frontal and posterior parietal regions.

In line with that, studies using neuromodulation showed that cathodal (hyperpolarizing) transcranial direct current stimulation over the posterior parietal cortex temporarily diminished non-painful phantom phenomena without affecting phantom pain, while anodal (depolarizing) stimulation over the motor cortex induced short-term reduction of phantom pain, with no alterations in non-painful phantom sensations (Bolognini *et al.*, 2013, 2015). An increased activation of posterior parietal and ventral premotor areas, but not SI, was also found during non-painful phantom sensations in a functional MRI-study with a congenital amputee (Brugger *et al.*, 2000). Björkman *et al.* (2012) found increased activation in bilateral SI as well as in posterior parietal and premotor cortices during tactile elicitation of phantom sensations at the residual limb in a functional MRI-study with six amputees and matched controls. The authors however, were not able to dissociate between brain activation related to stimulation of the residual limb versus the phantom sensations due confounding input from the residual limb nerves (Schady, Braune, Watson, Torebjörk, & Schmidt, 1994). In a recent functional MRI-study with five upper and

lower limb amputees and matched healthy controls, we found a distributed network comprising the ventral inferior cortex (BA44/45), the intraparietal sulci, the inferior parietal lobes and the secondary somatosensory cortices to be associated with non-painful phantom sensations (Andoh *et al.*, 2017). However, the sample of Andoh *et al.* (2017) was heterogeneous by including upper- and lower limb amputees and evoked phantom sensations were elicited at the residual limb and remote body sites. Moreover, the authors did not contrast brain activation during elicitation of phantom sensations with a matched stimulation in amputees. Thus, brain activation related to the stimulation could not be distinguished from brain activation specific for evoked phantom sensations.

The present study investigated the neural networks underlying evoked non-painful phantom sensations using functional MRI. Generalized psychophysiological interaction analysis (gPPI) was employed to study network properties involved in non-painful phantom sensation. Based on previous research on body illusions resembling the perception of non-painful phantoms (Ehrsson *et al.*, 2004, 2005), we expected evoked phantom sensation to be related with functional activation and connectivity in ventral frontal and posterior parietal areas. Furthermore, we expected significant activation of the secondary somatosensory cortex to be related with evoked phantom sensation since it show a somatotopy, which is compliant with phantom sensations elicited remote from the residual limb. Evoked phantom sensations were elicited at body sites other than the residual limb since local changes at the residual limb could confound the activation related to the evoked phantom sensation (Finnerup *et al.*, 2012; Schady *et al.*, 1994). We also differentiated activation related to the presence versus magnitude of phantom sensation (Davis *et al.*, 2015).

Materials and methods

Participants

Twelve unilateral major upper-limb amputees (mean age 47.83 years [*SD*=13.52, range: 23-70]; five female] and 12 healthy controls (mean age 47.50 years [*SD*=13.63, range: 24-70], five female) matched for sex, handedness and age participated in the study. The amputees in whom phantom sensations could be evoked remote from the residual limb, were acquired from an epidemiologic data

base (Bekrater-Bodmann *et al.*, 2015) of 3224 amputees. The amputees participated in a comprehensive psychometric assessment including a structured interview about the amputation and its consequences such as painful and non-painful phantom phenomena (Winter *et al.*, 2001) and the German version of the West Haven-Yale Multidimensional Pain Inventory (Flor *et al.*, 1990; Kerns *et al.*, 1985) modified to separately assess phantom and residual limb pain (Flor *et al.*, 1995). Fifty of 748 upper-limb amputees in the data base reported having evoked phantom sensations. These amputees took part in a telephone screening assessing MRI-compatibility and the presence and perceptual features of evoked phantom sensations. Amputees who reported to have phantom sensations that could be evoked from body sites remote from the residual limb were invited for a laboratory assessment of evoked phantom sensations and a subsequent MRI measurement performed at the same day.

Details on these participants are given in **Supplement S1.** Four of them had amputations on the right side, and five amputees were all-day prosthesis-users. All except for one amputee were right-handed before the amputation as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). One amputee was unable to report on her handedness. The participants had normal or corrected-to-normal vision, no history of neurological or mental disorder and did not use any centrally acting medication such as opiates. Prior to participation, they gave written informed consent in accordance with the Declaration of Helsinki. The study was approved by the ethics review board of the Medical Faculty Mannheim, Heidelberg University.

Laboratory assessment: Body topography of evoked phantom sensations

The topography of evoked phantom sensations was evaluated at 57 standardized body sites, employing a detailed assessment of perception in response to tactile and pinprick stimulation (**Fig. 1**) (Grüsser *et al.*, 2004). The stimuli were applied while the participants kept their eyes closed and were given in counterbalanced order for the two stimulation devices used: blunt and pointed metal rods, eliciting tactile and pinprick sensations. Each body site was stimulated three times for about 2 s with an inter stimulus interval of about 1 s. Then the amputees were instructed to report on the localization, quality and intensity of sensations felt at the stimulated site or anywhere else in the body. Evoked phantom sensations were defined as a sensation felt in the phantom limb, coinciding in time with the stimulation applied at the remote site. The body sites eliciting evoked phantom sensations were marked on the

subject's body, photographed and drawn into a 2D body template, in which the perceived location of the evoked phantom sensations in the phantom limb was indicated (**Fig. 1**). After stimulation of all body sites, we evaluated their spatiotemporal stability by re-testing the previously found body sites eliciting evoked phantom sensations with the blunt and pointed metal rods.

Stimulation techniques and body site selection for the functional MRI session

Body sites reliably eliciting evoked phantom sensations were further considered for the MRI-measurement. We used pneumatic or electrical stimulation in the subsequent MRI session. The decision to use either pneumatic or electrical stimulators was based on their efficacy to induce phantom sensations. Body sites reliably inducing evoked phantom sensations were first tested with non-painful pneumatic stimulation. In cases, were pneumatic stimulations were not capable of inducing phantom sensations, we used non-painful electrical stimulation. The stimulation was presented in a block design (eight blocks of stimulation alternating with blocks of rest, each lasting 27 s) to validate the stimulus-related on- and offset and the intensity of the evoked phantom sensations. As a control condition an anatomically homologous contralateral body site, not eliciting evoked phantom sensations, was chosen. In cases, where the contralateral body site was at the residual limb, below the amputation level or also eliciting evoked phantom sensations, an adjacent body site was chosen as a control site (**Fig. 1**).

For the tactile stimulation method (*N*=9 amputees), pneumatic stimulation was electronically controlled via a pneumatic relay device (MEG International Services Ltd., Coquitlam, Canada) set to a frequency of 1 Hz and pulse-width of 100 ms at 3 bars pressure and applied to the skin using pneumatic valve connected with a plastic tube to an elastic membrane (area 0.8 cm^2). The pneumatic stimulator was attached to the skin using medical tapes (Wienbruch, Candia, Svensson, Kleiser, & Kollias, 2006). For the electrical stimulation method, transcutaneous electrical stimulation (*N*=3 amputees) was applied using custom-made foil surface-electrodes. Monophasic constant current stimuli were applied for 200 μs duration at 1 Hz frequency at each block (DS7A, Digitimer, Hertfordshire, England). Perception and pain thresholds were obtained for each stimulated body site using the method of limits starting with a stimulus, which was not perceived to an intensity the participants indicated as '*perceivable*' (perception threshold). The stimulation was further increased to the

level the participant highlighted to be '*painful*' (pain threshold). The stimulation was further increased to the level of pain tolerance. This procedure was repeated three times. Finally, we delivered stimuli, which were at 60% between perception and pain threshold. The same stimulation parameters were used for the control body site and in the yoked controls.

Functional MRI

Experimental design

In the MRI, the amputees were measured in two conditions in counterbalanced order: Stimulation at a body site eliciting phantom sensations and stimulation at a control site, where we could not elicit phantom sensations. Each control person was yoked to an amputee and stimulated in the same order at anatomically homologous body sites in the MRI. The participants were tested in a block design consisting of eight blocks of stimulation alternating with blocks of rest, each lasting 27 s. Each block was followed by a rating on a visual analogue scale lasting 15 s assessing the intensity of evoked phantom sensations during the preceding stimulation or rest block with the endpoints '*no sensation*' to '*most intense*'. The questions were as follows: "*How intense was your perception of the stimulation in your missing limb during the stimulation/during rest*?" Since it was possible that the evoked phantom sensations did not completely resolve after stimulus-offset, the intensity of evoked phantom sensations was also assessed during rest. In the yoked controls, the visual analogue scale captured the perceived stimulation intensity, ranging from '*no sensation*' to '*most intense*'. The questions were as follows: "*How intense was your perception of the stimulation at the stimulated site during the stimulation/during rest*?"

After each MRI session ratings on the perceived sensations were assessed using a numerical rating scale. Moreover, the participants were asked to report on any sensation remote from the stimulation site to ensure validity of the control conditions. The participants were asked to rate the perceived intensity and valence of the stimulation at the stimulated site. The amputees were further asked to rate the intensity and valence of evoked phantom sensations. Ratings ranged from 0 '*no sensation*' to 10 '*most intense sensation*' for the intensity and from -10 '*very unpleasant*' to 10 '*very pleasant*' for the valence ratings.

MRI data acquisition

A MAGNETOM TRIO 3 T scanner (Siemens AG, Erlangen, Germany) with a 32-channel head coil was used to obtain 230 whole-brain gradient-echo echo planar images (EPI) with a blood oxygen level-dependent (BOLD) contrast (TR/TE=3000/27 ms; flip angle=90°, matrix=128x128, voxel size=1.5x1.5x2 mm, GRAPPA factor=3, 40 slices). In the same session, a high-resolution T1-weighted 3D image was recorded (TR/TE=2300/2.98 ms; 192 contiguous slices; matrix=248x256; voxel size=1 mm^3, bandwidth=1.184 Hz/pixel). Stimulation events were synchronized with functional volume acquisition using Presentation software (version 15.0, www.neurobs.com). Additionally, a double echo gradient sequence was used to acquire a static B_0-fieldmap (TR=468 ms; short/long TE=4.92/7.38 ms; matrix=96x96; voxel-size=2x2x3 mm) to enable correction of geometrical distortions in functional images.

Functional MRI data analysis

Preprocessing

The functional MRI data were analyzed using tools from FMRIB's Software Library (FSL, v. 5.02) (Smith *et al.*, 2004). The first three functional volumes were discarded prior to preprocessing to account for T1-equilibration effects. Preprocessing comprised B_0-fieldmap-based unwarping of echo planar images using PRELUDE+FUGUE, intra-modal motion correction using MCFLIRT (Jenkinson *et al.*, 2002), slice-timing correction, mean-based intensity normalization, spatial smoothing using a Gaussian kernel with 5 mm full width at half maximum, and high-pass temporal filtering at σ=100 s. Registration was performed in two steps: Functional volumes were spatially realigned to the high-resolution T1-weighted volume, where non-brain structures were removed using the Brain Extraction Tool (BET) (Smith, 2002). Functional volumes were then registered to the standard MNI152 template (Montreal Neurological Institute, Montreal, Canada) using non-affine FNIRT-registration (Andersson *et al.*, 2007) with a warp-resolution of 8 mm. Time-series statistical analysis was performed with the pre-whitening tool of FMRIB's Improved Linear Model (FILM) with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001).

Statistical analysis

The statistical analysis was carried out using the fMRI Expert Analysis Tool (FEAT v. 6.00) (www.fsl.fmrib.ox.ac.uk). Each session for a given participant was modeled separately at the first level. The stimulation epochs were modeled as event of interest. The rating epochs and six motion parameters were modeled as events of no interest and nuisance, respectively. The event types were convolved with a double-gamma function to model the hemodynamic response function with their first-order temporal derivatives. Group statistics were computed using FMRIB's Local Analysis of Mixed Effects (FLAME 2) (Beckmann, Jenkinson, & Smith, 2003). Clusters of significant brain responses were determined using a $z > 2.3$ threshold and a corrected cluster threshold of $p=0.05$ assuming a Gaussian random field for the z-statistics. Significant clusters were labeled using the probabilistic Jülich-Histological (Eickhoff *et al.*, 2007) and Harvard-Oxford Atlases (www.cma.mgh.harvard.edu).

Brain areas related to evoked phantom sensations

We differentiated between the *neural correlates of evoked phantom sensations* and the *neural correlates of the perceived intensity of evoked phantom sensations.* Whereas the former reflects mechanisms related to the presence versus absence of a sensation, the latter might reflect a more general 'magnitude coding' not necessarily specific for evoked phantom sensations (Baliki, Geha, & Apkarian, 2009).

Thus, brain activation specific for the presence or absence of evoked phantom sensations was determined by contrasting brain activation during elicitation of evoked phantom sensations with a control stimulation, which did not elicit evoked phantom sensations. This comparison was made within amputees using a phantom sensation free control site and compared to yoked healthy controls who were stimulated at homologous body sites.

In the within-subjects comparison, the brain responses were contrasted between the evoked phantom sensation and control body site (evoked phantom sensations > control site) using fixed-effects analysis followed by a third-level mixed-effects analysis (Beckmann *et al.*, 2003) to average the single-subject contrasts. In the between-group comparison, the brain responses were contrasted between the evoked phantom sensation condition in the amputees and the anatomically matched

stimulation in the yoked controls (evoked phantom sensations amputees > yoked controls) using an unpaired t-test.

To delineate brain regions with conjoint activation for both contrasts of interest (evoked phantom sensations > control site AND evoked phantom sensations amputees > yoked controls), we applied conjunction analysis (Friston, Penny, & Glaser, 2005) employing cluster-based inference as enabled by easythresh_conj (www2.warwick.ac.uk/fac/sci/statistics). Regions of conjoint activation were expected to reveal specificity for the encoding of evoked phantom sensations.

We also investigated the neural correlates of the perceived intensity of the evoked phantom sensation and the non-painful sensation at the stimulated body site, potentially reflecting a more general magnitude coding. Therefore, brain activation was correlated with the demeaned ratings on the intensity perceived at the stimulated site and in the phantom limb. We also investigated whether the elicitation of phantom sensations was linked to activation in the contralateral SI. Due to differences in the perceived localization of evoked phantom sensations as well as side of amputation, we computed subject-wise contrast between the evoked phantom sensation and control site stimulation to check for SI activations contralateral to amputation.

Effective connectivity analysis

Effective connectivity was computed with bivariate regressive generalized psychophysiological interaction analysis (gPPI) using the seed-driven approach in the CONN toolbox v.16b (Whitfield-Gabrieli & Nieto-Castanon, 2012) as implemented in SPM8 (www.fil.ion.ucl.ac.uk/spm). In gPPI the task-dependent directional influences between pairs of regions of interest (ROIs) are estimated (McLaren, Ries, Xu, & Johnson, 2012; Whitfield-Gabrieli & Nieto-Castanon, 2012). gPPI was performed using the evoked phantom sensations > control site contrast, which was expected to show high specificity for evoked phantom sensations.

In total, 94 ROIs originating from the Juelich-Histological Atlas were used as atlas ROIs. In addition, one functional ROI covering parts of the left ventral premotor and inferior frontal cortices (BA44/45) and one functional ROI covering the anterior insula were included. These functional ROIs were derived from the conjunction analysis. Based on the imaging literature on crossmodal integration in peripersonal space (Ehrsson *et al.*, 2005; Grivaz *et al.*, 2017), ROIs in the ventral premotor and inferior

frontal cortices as well as the posterior parietal cortex were modeled as seed regions and connectivity was computed across all ROIs. Information on seed and atlas ROIs is given in **Supplement S2**.

Preprocessing was performed based on the SPM8 preprocessing routines comprising motion correction, unwarping, slice-timing correction, co-registration of the functional images to the anatomical images, intensity normalization, non-affine co-registration to the MNI152 template, and spatial smoothing using a Gaussian kernel of 5 mm full width at half maximum. Connectivity was assessed based on Fisher-transformed correlation coefficients at the group level (Whitfield-Gabrieli and Nieto-Castanon, 2012).

The average time series was computed across all voxels within each ROI and high-pass filtered at $\sigma=100$ s. The CONN toolbox employs anatomically informed component-based noise correction ("aCompCor"), correcting for physiological and other sources of noise by regressing-out signals, for example, from the white matter or cerebrospinal-fluid (Behzadi, Restom, Liau, & Liu, 2007). The task regressors were convolved with a double-gamma function and their first-order temporal derivatives and modeled as confound regressors. To control for multiple comparisons, ROI-to-ROI-effects were determined at a seed-level false discovery rate threshold of $p<0.05$.

Analysis of perceived sensations

The ratings on the percepts at the stimulated body site and in the phantom were analyzed using R (R Development Core Team, 2015) and figures were created using the ggplot2 package (Wickham, 2009). Linear mixed models were carried out using the lme4 package (Bates, Maechler, Bolker, & Walker, 2014) with maximum-likelihood estimation. Satterthwaite's approximation was used to estimate the degrees of freedom as implemented in the lmerTest package (Kuznetsova, Brockhoff, & Christensen, 2014). The individual cases were specified as a random intercept.

In the evoked phantom sensation condition, the ratings on the intensity and valence felt at the stimulated body site were correlated with ratings on the intensity and valence perceived in the phantom. Moreover, we tested whether the ratings on intensity felt at the stimulated body site differed between the evoked phantom sensation and control conditions without stimulus-induced phantom sensations.

The block-wise visual analogue scale ratings on the intensity of evoked phantom sensations assessed during the MRI-session were transformed to a scale with the endpoints 0 '*no sensation*' and 10 '*most intense sensation*'. To investigate whether the evoked phantom sensations could be reliably turned on and off, we modelled the within-subject factors STIMULATION (rest/stimulation) and BLOCK (block 1 to 8) and checked for significant differences in STIMULATION. Moreover, we contrasted the first and last stimulation trial to investigate habituation effects in the perceived intensity of evoked phantom sensations.

Correlational analysis was performed using Pearson correlation. Kendall's tau was used when assumption of normality was not fulfilled. Normality of the data was checked using the Shapiro-Wilk test. All models were carried out with two-sided significance thresholds set at p=.05.

Results

Laboratory assessment: body topography of evoked phantom sensations

Evoked phantom sensations with a stimulus-related on- and offset were found in all amputees (**Fig. 1**). In 10 of the 12 amputees, evoked phantom sensations could be elicited from body sites contralateral to the amputation (**Fig. 1**: in A4 and A6 only from the side ipsilateral to the amputation). In four amputees, evoked phantom sensations could be elicited from the legs (**Fig. 1**: A: 2, 3, 5, 12). Moreover, four amputees showed mirror referrals (Giummarra *et al.*, 2011), in which the body site eliciting evoked phantom sensations was on the intact limb at the anatomically same site as the evoked phantom sensation in the phantom (**Fig. 1**: A: 2, 3, 8, 12). In six amputees evoked phantom sensations could be elicited from the residual limb (**Fig. 1**: A: 1, 2, 3, 5, 9, 10). In one amputee evoked phantom sensations could be evoked at all ventral body sites tested (**Fig. 1**: A: 2). In most of the amputees, the quality of evoked phantom sensations differed from the quality usually linked to the stimulation method used. For example, the tactile stimulation delivered via the pneumatic stimulator were associated with various types of evoked phantom sensations comprising a pulling sensation (A: 10), tingling sensations (A: 3, 5-9, 11) or the feeling that the phantom started to swell (A: 12) (**Table 1).**
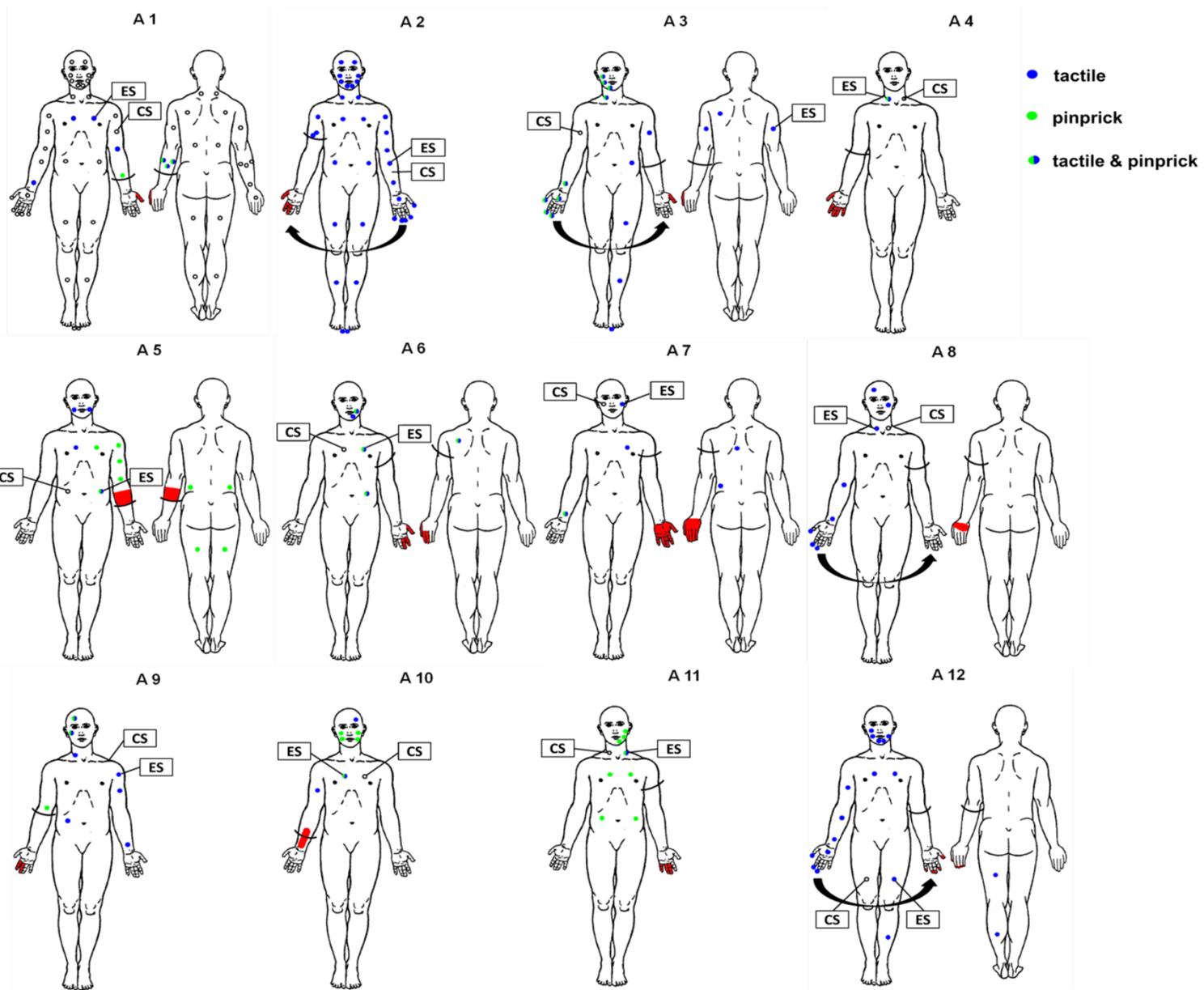
A 1   A 2   A 3   A 4

A 5   A 6   A 7   A 8

A 9   A 10   A 11   A 12

ES
CS

tactile
pinprick
tactile & pinprick

63

Figure 1 Body topography of evoked phantom sensations Body templates with 57 standardized body sites stimulated (outlined circles, for illustration only shown for subject A1) to investigate the topography of body sites eliciting evoked phantom sensations for each amputee (A 1-12). ES=elicitation site; stimulated in the MRI to induce evoked phantom sensations with corresponding evoked phantom sensations marked as red shaded area. CS=control site; stimulated in the MRI as control site without evoked phantom sensations. Blue dots=evoked phantom sensations could be elicited by blunt metal rods; Green dots=evoked phantom sensations could be elicited by pointed metal rods; Blue and green dots=evoked phantom sensations could be elicited by blunt and pointed metal rods. Red shaded areas mark the perceived location of the evoked phantom sensations in the phantom limb and the intersection line marks the level of amputation. The black arrows in A: 2, 3, 8 and 12 mark amputees with mirror referrals. Body templates were adapted from Grüsser *et al.* (2004).

Functional MRI session

Perceived sensations

The intensity perceived at the stimulated body site did not significantly differ between the evoked phantom sensation (*M*=6.25, *SD*=3.19) and the control condition (*M*=6.92, *SD*=2.71) in the amputees (*t*(11)=0.71, p=0.49) (**Table 1**). Moreover, the intensity perceived at the stimulated body site did not significantly differ between the amputees and the yoked controls (*M*=6.09, *SD*=2.97) stimulated at homologous body sites (*t*(22)=-0.14, p=0.89) (**Table 1;Supplement S3**).

Correlational analysis showed that the intensity (*r*(10)=0.10, p=0.75) and the valence (*tau*(10)=0.05, p=0.85) of the stimulation felt at the stimulated body site were not significantly related to the intensity of the evoked phantom sensations (**Table 1**). The intensity (*tau*(10)=0.11, p=0.65) and the valence (*tau*(10)=0.42, p=0.12) perceived at the stimulated body site did also not significantly correlate with the valence perceived in the phantom (**Table 1**). On average, the evoked phantom sensations were rated with moderate intensity (*M*=5.67, *SD*=2.81) and to be neutral in valence (*M*=-0.42, *SD*=2.68) (**Table 1**).

In the linear mixed model the factor STIMULATION predicted significantly the intensity of evoked phantom sensations (*F*(1,165)=401.12, *p*<0.001) with significantly higher ratings during the stimulation (*M*=5.85, *SD*=2.84) than during the rest (*M*=1.4, *SD*=1.83) blocks (*t*(165)=7.25, *p*<0.001) (**Fig. 2**). The factor BLOCK (*F*(7,165)=0.54,

p=0.80) and the STIMULATION-by-BLOCK interaction (F(7,165)=0.16, *p*=0.99) did not significantly predict the intensity of evoked phantom sensations. Contrasting the perceived intensity of evoked phantom sensations between the first (*M*=6.05, *SD*=2.68) and last (*M*=5.48, *SD*=2.99) stimulation block, we did not find significant habituation effects (*t*(11)=-0.83, *p*=0.42). The yoked controls and the amputees did not report on stimulation related sensations remote from the stimulated site during the control stimulation.

Table 1 Perceptual qualities and intensities reported by the amputees subsequent to the elicitation of evoked phantom sensations (EPS) condition in the MRI.

Amputee	Stimulation method	Intensity at stimulated body site	Valence at stimulated body site	EPS quality	Intensity of EPS	Valence of EPS	EPS location
A1	electric	8	0	non-painful, soft electrical currents	8	0	D1
A2	pneumatic	4	0	non-painful, loosening of a cramping sensation, movements, pleasant	8	-5	D1-D3
A3	pneumatic	10	0	non-painful, tingling	6	-1	D1
A4	electric	10	0	non-painful, pressure	6	-5	D1-D5
A5	electric	10	-3	non-painful, tingling	1	2	forearm
A6	pneumatic	10	0	non-painful, tingling	8	0	D1-D3
A7	pneumatic	6	0	non-painful, tingling	4	0	whole hand
A8	pneumatic	2	0	non-painful, tingling	3	0	volar

A9	pneumatic	5	0	non-painful, tingling	3	-1	D2-D3
A10	pneumatic	4	2	non-painful, dragging sensation	3	0	forearm
A11	pneumatic	2	0	non-painful, tingling	10	0	D3-D5
A12	pneumatic	4	-3	non-painful, swollen sensation	8	5	D1-D5
Mean/Median		6.25/5.5	-0.33/0		5.67/6	-0.42/0	
±SD		3.19	1.37		2.81	2.68	

The intensity and valence were assessed using a numerical rating scale. Intensity ratings ranged from 0 '*no sensation*' to 10 '*most intense sensation*' and valence ratings ranged from -10 '*very unpleasant*' to 10 '*very pleasant*'. D1-D5=digits from the first (D1) to the fifth (D5) digit.
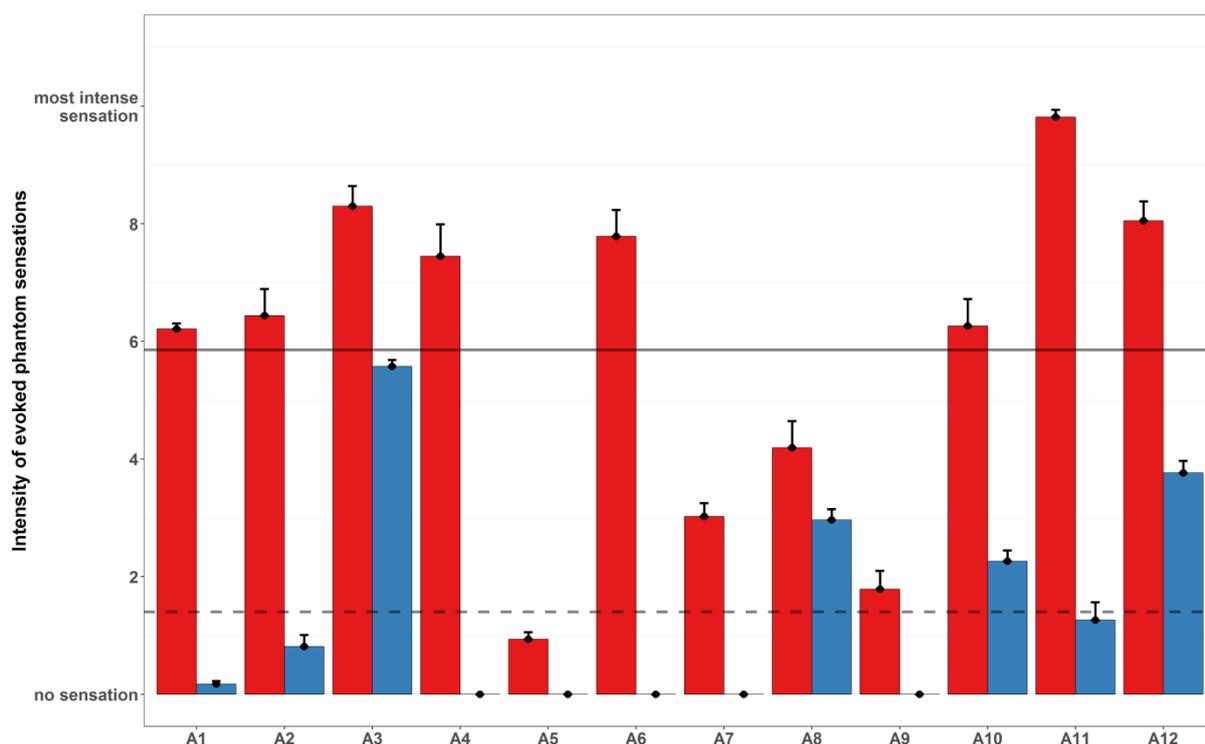
Figure 2 Intensity of evoked phantom sensations across amputees. Bar-error-bar plot (*M±SEM*) showing the mean intensity of evoked phantom sensations across stimulation (red) and rest (blue) blocks for each amputee (A1-A12). The average intensity of evoked phantom sensations across all amputees is shown during stimulation (solid line) and rest (dashed line) blocks. The intensity of evoked phantom sensations was rated on a visual analogue scale ranging from '*no sensation*' to '*most intense sensation*' after each of the eight stimulation and rest blocks. The visual analogue scale ratings were transformed to a scale with the endpoints 0 '*no sensation*' and 10 '*most intense sensation*'.

Brain areas related to evoked phantom sensations

The contrast between stimulation at a body eliciting phantom sensations and a control body site without phantom sensations (evoked phantom sensation > control site) showed significantly increased activation in the left ventral premotor and inferior frontal cortices (BA44/45), the left anterior insula and left basal ganglia (caudate nucleus, putamen). Moreover, significantly increased activation was found in the bilateral secondary somatosensory cortices (OP1, OP4) and the right supramarginal gyrus (**Table 2, Fig. 4**).

The between-group comparison (evoked phantom sensations amputees > yoked controls) also showed increased activation in left ventral premotor and inferior frontal

cortices (BA44/45), the left anterior insula, the left caudate nucleus and putamen as well as the left secondary somatosensory cortex (OP1, OP3) (**Table 2, Fig. 4**). Moreover, significantly increased activation was found in the left posterior parietal (anterior intraparietal sulcus, BA2) and cerebellar regions (**Table 2, Fig. 4**). No significant differences were found when brain responses between the control site in amputees and the matched body site in yoked controls were contrasted.

The conjunction analysis including the within-amputee (evoked phantom sensations > control site) and the between-group (evoked phantom sensations amputees > yoked controls) contrasts showed increased activation in the left ventral premotor and inferior frontal cortices (BA44/45), the left anterior insula and basal ganglia (caudate nucleus and putamen) (**Fig. 4**).
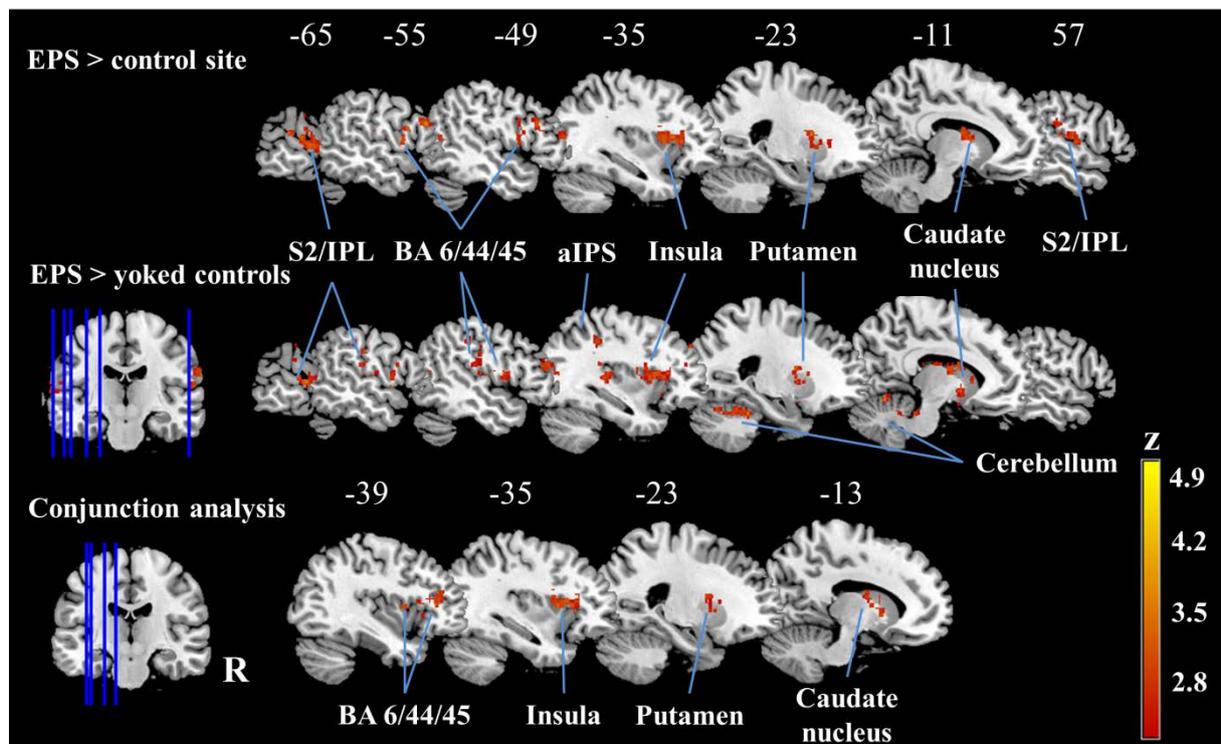
Figure 4 Brain responses during the evoked phantom sensations (EPS) versus the control conditions. A. Brain regions showing increased activation during stimulation at the evoked phantom sensations versus control site in amputees (evoked phantom sensations > control site). **B.** Brain regions showing increased activation in amputees during stimulation at the evoked phantom sensations versus matched body site in yoked controls (evoked phantom sensations amputees > yoked controls). **C.** Brain regions showing increased activation during evoked phantom sensations compared to both control conditions (evoked

phantom sensations > control site AND evoked phantom sensations amputees > yoked controls).

S2=secondary somatosensory cortex; IPL=inferior parietal lobe; aIPS=anterior intraparietal sulcus; R=right hemisphere. Activations are overlaid on the MNI template as provided by mricron.

Table 2 Peak coordinates and brain regions showing significantly increased activation during stimulation of evoked phantom sensation (EPS) versus control conditions.

Region (Peak voxel)	MNI [mm] x	y	z	z-score	cluster extent [voxel]	Region (Peak voxel)	MNI [mm] x	y	z	z-score	cluster extent [voxel]
EPS > control site						**EPS > yoked controls**					
Inferior frontal gyrus, pars triangularis	-54	26	24	3.64	993	Frontal pole	-44	50	16	4.3	1622
Putamen	-22	6	14	3.62		Anterior insula	-30	14	12	4.01	
Inferior frontal gyrus, pars triangularis	-40	34	10	3.58		Frontal pole	-40	44	28	4	
Anterior insula	-28	18	12	3.55		Caudate nucleus	-12	8	2	3.97	
Caudate nucleus	-18	6	16	3.47		Anterior insula	-36	22	-2	3.76	
Central operculum	-36	8	8	3.41		Precentral gyrus (BA6)	-58	6	10	3.65	
Precentral gyrus (BA6)	-64	6	8	3.56	426	Parietal operculum (OP1)	-40	-30	20	4.67	709
	-52	8	20	3.47			-42	-26	20	3.85	
Parietal operculum (OP4)	-66	-28	16	3.41		Central operculum	-46	-18	22	3.6	

Region	x	y	z	z-stat	Size	Region	x	y	z	z-stat	Size
						(OP3)					
Parietal operculum (OP1)	-66	-8	6	3.41		Postcentral gyrus (BA2)	-46	-38	50	3.52	
	-64	-16	12	3.4		Central operculum (OP4)	-58	-12	16	3.49	
Precentral gyrus (BA6)	-42	2	28	3.31		Central operculum (OP3)	-46	-16	16	3.38	
Parietal operculum (OP1)	60	-14	14	3.42	396	Cerebellum (Vermis)	-8	-62	-12	3.98	486
	48	-14	12	3.36			-14	-52	-20	3.81	
Supramarginal gyrus, anterior	66	-22	26	3.3			-18	-52	-22	3.7	

Clusters of significant brain responses were determined using a $z > 2.3$ threshold and a corrected cluster threshold of $p=0.05$ assuming a Gaussian random field for the z-statistics.

Mean brain activations during the evoked phantom sensations and control site condition in amputees

During the elicitation of evoked phantom sensations, significant clusters of activation were found bilaterally in the secondary somatosensory cortices. The cluster with the peak in the right secondary somatosensory cortex (OP1, OP4) extends into the inferior parietal lobe (supramarginal gyrus). The cluster with the peak in the left secondary somatosensory cortex extends into the left ventral premotor (BA6) and inferior frontal cortices (BA44/45) (**Fig. 3, Supplement S4**). During stimulation of the control site, significant activations were also found bilaterally in the secondary somatosensory cortices (OP1, OP4). Moreover, activations were observed in the middle frontal gyrus, the frontal pole, the cingulate cortex, the dorsal premotor cortex, inferior parietal regions and the precuneus (**Fig. 3, Supplement S4**). In both conditions, deactivations were found in primary and higher-order visual areas (BA17/18 and the lateral occipital cortex).

Moreover, we observed activation in SI contralateral to the amputation in 9 out of 12 amputees (**Supplement S4**). However, SI-activation in amputee A8 (x,y,z: 20,-36,74) was more posterior mainly covering BA2 (**Fig. 5**).
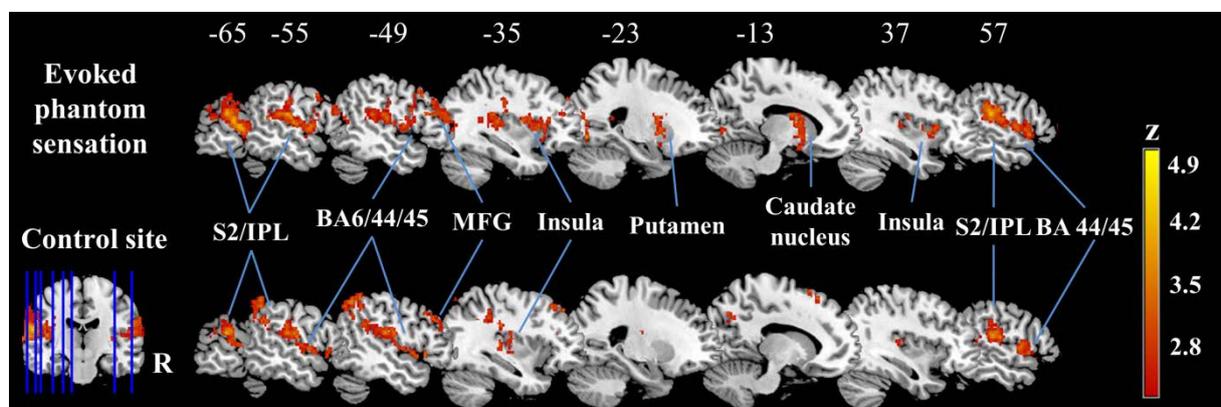
Figure 3 Mean brain activations during evoked phantom sensations and sensation at control site in amputees.

MFG=middle frontal gyrus; S2=secondary somatosensory cortex; IPL=inferior parietal lobe; BA6=premotor cortex; BA44/45=inferior frontal gyrus; R=right hemisphere. Activations are overlaid on the MNI template as provided by mricron.

Correlation between brain activation and ratings on the perceived intensity at the stimulated site and in the phantom limb

The brain activation correlated significantly with the stimulation intensity in the right posterior insula and secondary somatosensory cortex. The intensity of evoked phantom sensations correlated significantly with brain activation in the thalamus, cerebellum and caudate nucleus **(Table 3)**.

Table 3 Peak coordinates of brain regions showing significant correlation with the intensity perceived at the stimulation site and in the phantom.

Region	MNI [mm] x	y	z	z-score	cluster extent [voxel]	Region	MNI [mm] x	y	z	z-score	cluster extent [voxel]
Intensity of evoked phantom sensations						**Intensity of stimulation**					
Temporal fusiform cortex	-32	-36	-16	4.29	334	Central operculum (OP3)	42	-14	22	5.65	1365
Cerebellum (V)	-24	-42	-20	4.04		Posterior insula (Ig2)	40	-16	8	5.51	
Cerebellum (VI)	-24	-62	-20	3.57		Parietal operculum (OP1)	52	-26	20	5.26	
Thalamus	6	-22	16	5.27	304	Parietal operculum (OP4)	64	-14	18	5.08	
Caudate nucleus	-14	-10	22	4.14		Central operculum (OP1)	60	-18	14	4.97	
	-12	0	16	3.62		Inferior parietal lobule (PFop)	48	-28	30	4.69	

Clusters of significant brain responses were determined using a $z > 2.3$ threshold and a corrected cluster threshold of $p=0.05$ assuming a Gaussian random field for the z-statistics.

Effective connectivity analysis

The regressive gPPI-analysis revealed a widespread fronto-parietal network (**Fig. 6, Table 4**). Within this network, seven seed regions were found to exert a positive influence on other regions of the fronto-parietal network. Four seeds in the left and right posterior parietal cortices [right: posterior angular gyrus and superior parietal lobe (BA5); left: superior parietal lobe (BA5)] were shown to increase brain activation in other posterior parietal areas intra- or inter-hemispherically. The three seeds in the left (functional ROI in BA6/44/45) and right frontal cortices (BA44 and BA45) exerted a positive influence on the same region in the left superior parietal lobe (BA7) (**Fig. 6, Table 4**).

Figure 6 A fronto-parietal network specific for evoked phantom sensations as identified by regressive generalized psychophysiological interaction analysis. Render brain (left) and connectome ring (right) illustration ROI-to-ROI connectivity determined from the evoked phantom sensations > control site contrast within amputees. Render brain: Seed regions exerting significant influence on other brain regions are shown with red-shaded labels and linked regions in the network are shown with blue-shaded labels. ROI-to-ROI-effects were thresholded at a seed-level false discovery rate of $p<0.05$ and mapped on a MNI surface render brain as provided by CONN v16b (Whitfield-Gabrieli & Nieto-Castanon, 2012). Connectome ring: The strength of task-dependent ROI-to-ROI connectivity is illustrated by hot-cool colour map conduits based on *t*-scores. Position of the ROIs is illustrated on render brains in sagittal view surrounding the connectome ring.

Subregions of the superior parietal lobe (SPL): 5L, 5M, 7A, 7M, 7P, 5Ci; Subregions of the inferior parietal lobe (IPL): angular gyrus (Pga, Pgp), supramarginal gyrus (PF, PFm, PFcm); aIPS hIP1=anterior intraparietal sulcus; fROI (ventral premotor cortex)=functional ROI from the conjunctions analysis covering BA6/44/45; L=left hemisphere.

Table 4 Fronto-parietal network specific for evoked phantom sensations identified by regressive generalized psychophysiological interaction analysis.

Seed ROI	Hemisphere	*t*-score	Linked ROI	Hemisphere	*p*(FDR)
1. IPL(Pga)	Right	$t(11)=6.35$	SPL(5M)	Left	0.005
		$t(11)=5.50$	SPL(5Ci)	Right	0.005
		$t(11)=5.50$	SPL(5L)	Left	0.005
		$t(11)=5.11$	SPL(7A)		0.007
		$t(11)=4.42$	SPL(5Ci)		0.017
		$t(11)=3.71$	SPL(7P)	Left	0.047
		$t(11)=3.64$	SPL(5M)	Right	0.047
2. SPL(5L)	Left	$t(11)=6.03$	SPL(5Ci)	Left	0.007
		$t(11)=5.54$	IPL(PF)		0.008
		$t(11)=4.72$	SPL(5M)	Right	0.015
		$t(11)=4.64$	IPL(PFm)	Left	0.015
		$t(11)=4.46$	IPL(PFcm)	Right	0.016
		$t(11)=4.11$	IPL(Pga)		0.025
		$t(11)=3.49$	SPL(7M)		0.045
		$t(11)=3.48$	aIPS (hIP1)		0.049
3. SPL(5L)	Right	$t(11)=4.69$	IPL(PF)	Right	0.049
		$t(11)=4.32$	IPL(PFm)		0.049
		$t(11)=4.01$	SI(BA3a)		0.049
		$t(11)=3.94$	IPL(PFcm)		0.049

4. SPL(5M)	Left	$t(11)=7.03$	IPL(PFm)	Right	0.002
		$t(11)=5.64$	IPL(Pga)		0.004
		$t(11)=5.63$	IPL(PF)		0.004
		$t(11)=4.16$	aIPS (hIP1)		0.034
		$t(11)=3.89$	IPL(PFcm)		0.043
5. BA45	Right	$t(11)=5.38$	SPL(7P)	Left	0.019
6. fROI(BA6/44/45)	Left	$t(11)=4.73$	SPL(7P)	Left	0.049
7. BA44	Right	$t(11)=4.99$	SPL(7P)	Left	0.035

ROI-to-ROI-effects were thresholded at a seed-level false discovery rate (FDR) of p<0.05. Subregions of the superior parietal lobe (SPL): 5L, 5M, 7A, 7P, 5Ci; Subregions of the inferior parietal lobe (IPL): angular gyrus (Pga, Pgp), supramarginal gyrus (PF, PFm, PFcm); aIPS hIP1=anterior intraparietal sulcus; fROI(BA6/44/45)=functional ROI from the conjunction analysis covering BA6/44/45.

Discussion

The phenomenon of evoked phantom sensations has been reported for centuries (Mitchell, 1872), but the neural mechanisms of evoked phantom sensations need to be examined in more detail (Giummarra & Moseley, 2011). We were able to induce phantom sensations with a stimulation-related on and offset in 12 amputees. The non-painful phantom sensations were related to increased activation in the left ventral frontal cortex, the left insula and putamen. Moreover, we found increased activation in the right inferior parietal lobe and the bilateral secondary somatosensory cortices when contrasting brain activation between the evoked phantom sensation and control condition in amputees. Regressive psychophysiological interaction analysis further showed increased connectivity between bilateral ventral frontal cortices and bilateral posterior parietal regions.

Fronto-parietal brain activation and connectivity

The rubber hand illusion is associated with increased activation in the ventral premotor, intraparietal sulci and cerebellar regions (Ehrsson *et al.*, 2004, 2005). Despite of substantial reorganization following deafferentation, amputees have been shown to activate the same regions during the rubber hand illusion (Schmalzl, Kalckert, Ragnö, & Ehrsson, 2014). We found that amputees also showed increased activation in ventral inferior (premotor and BA44/45) and posterior parietal areas (inferior parietal and intraparietal cortex) during elicitation of non-painful phantom sensations. In our recent study, significantly increased activation in the ventral inferior and inferior and intraparietal cortex was also found to be associated with non-painful phantom sensations (Andoh *et al.*, 2017).

Guterstam *et al.* (2013) used a modified version of the rubber hand illusion to induce the perception of feeling touch on a supernumerary limb. Therefore the experimenter stroked synchronously the hidden actual hand and a portion of empty space in the near-reach space of the participant. The authors investigated the neural circuitry underlying this 'invisible hand illusion' showing increased task-dependent connectivity between the left ventral frontal and the left posterior parietal areas to be linked with the strength of the illusion. We also found increased ventral frontal-posterior parietal coupling during evoked phantom sensations using regressive gPPI-analysis. The bilateral ventral frontal cortex (BA44/45) showed increased connectivity with the right superior parietal cortex. Furthermore, increased connectivity was found between

various intra- and interhemispheric posterior parietal regions. Thus, commonalities in brain activation and connectivity between body illusions inducing the perception of having a supernumerary limb (Guterstam *et al.*, 2013) or owning a rubber hand indicate similar neural mechanisms.

Insula and putamen

In the conjunction analysis as well as the contrast between the evoked phantom sensation and control site stimulation in amputees, we found significant activation in the left anterior insula and putamen. In a functional MRI-study contrasting imagined versus actual touch at the dorsum of the right hand, significantly increased activation in the left putamen and insula was also found to be related with mental imagery of touch (Yoo, Freeman, McCarthy, & Jolesz, 2003). In line with our findings, the authors further reported increased activation in the left inferior ventral cortex (BA 44) and the primary and secondary sensory cortices during imagery of touch. Besides a prominent involvement of posterior parietal and ventral premotor regions in the crossmodal integration of bodily signals (cf., Blanke *et al.*, 2015), the left putamen has also been shown to be important for the integration of the multimodal representation of the hand (Gentile, Guterstam, Brozzoli, & Ehrsson, 2013).

Secondary somatosensory cortex

Replicating previous findings (Knecht *et al.*, 1996; Borsook *et al.*, 1998; Grüsser *et al.*, 2004), we found non-painful phantom sensations elicited from body sites contralateral to amputation (*N*=10) or even from the legs (*N*=4 amputees) in upper-limb amputees. Since the secondary somatosensory cortex shows a larger reorganizational potential and a different topography than SI (Pons, Garraghty, & Mishkin, 1988), we and others (Flor *et al.*, 2000; Grüsser *et al.*, 2004) hypothesized that the secondary somatosensory cortex might be a neural correlate of phantom sensations elicited remote from the residual limb. In line with that, we found increased activation in the secondary somatosensory cortices when contrasting evoked phantom sensation with the control condition in amputees. Taoka *et al.* (2016) investigated body maps in the secondary somatosensory cortex using single-unit recordings in awake macaques. The authors found that 282 from 1099 recorded neurons possessed multiple body region receptive fields with a continuous extension of trunk receptive fields into distal limb regions. Here, we observed that in half of the amputees phantom sensations could be elicited at trunk sites. Moreover, Taoka *et al.*

(2016) found that distal parts of the upper and lower limbs were highly interconnected fitting to our observation that phantom sensations could be elicited at the ipsilateral or contralateral leg in four amputees (see also: Grüsser *et al.*, 2004). The stimulation intensity was matched between the evoked phantom sensation and the control conditions, excluding the possibility of secondary somatosensory cortex activation driven merely by the stimulation.

Correlation between perceived intensities and brain activation

The perceived intensity of evoked phantom sensations was significantly positively correlated with brain activation in the cerebellum. Ehrsson *et al.* (2005) found a positive correlation between the strength of the rubber hand illusion and brain activation in cerebellar regions further indicating similarities between non-painful phantom sensations and rubber hand illusions. Furthermore, a significant positive correlation with non-painful phantom sensation was found in the right secondary somatosensory and inferior parietal cortex. Andoh *et al.* (2017) also found increased activation in secondary somatosensory and inferior and intraparietal lobe. They observed a significant positive correlation between activation in the right intraparietal sulcus and the intensity of evoked phantom sensation. However, they did not report on activation in the right inferior parietal lobe and intensity ratings.

We also found a positive correlation between the perceived intensity at the stimulated body site and activation in the right posterior insula and the primary and secondary somatosensory cortices. Baliki *et al.* (2009) found intensity ratings as well as painful sensations to be related with activation in parts of the insular cortex indicating that this region might be involved in more general magnitude coding (cf., Davis *et al.*, 2015).

Conclusion

Experiments inducing similar illusory percepts such as supernumerary phantom limbs, imagined touch, or referral of touch to an empty portion of space refer to similar patterns of brain activation and connectivity as found during the evocation of non-painful phantom sensations in this study. This network comprises brain regions discussed to be important for the monitoring of crossmodal conflicts (BA44/45) (Fink *et al.*, 1999) as well as posterior parietal regions known to be important for a coherent multimodal perception and localization of body parts such as a phantom, a supernumerary limb or a rubber hand (Apps et al., 2015; Makin, Holmes, & Zohary,

2007). Moreover, phantom sensations elicited remote from the residual limb were associated with significantly increased activation in secondary somatosensory cortices, which might reflect the higher reorganizational potential and different topography of body maps in this brain area.

Body illusions are not only a matter of scientific curiosity, but have been shown to offer successful therapeutic interventions to relief pain or recover motor function in otherwise treatment resistant chronic pain conditions including phantom pain (Foell *et al.*, 2014). Knowledge about the contextual factors and neural networks underlying non-painful phantom sensations might help to develop novel treatments to decrease phantom pain or gain prosthesis control. Evoked phantom sensations have already been used to develop a movement-free visuo-tactile version of mirror therapy (Schmalzl, Kalckert, Ragnö, & Ehrsson, 2013) or to improve the acceptance and usage of prosthesis (Rosén *et al.*, 2009). The use of prosthetic devices has been shown to be associated with less cortical reorganization and a reduction in phantom pain (Lotze *et al.*, 1999; Dietrich *et al.*, 2012; Preißler *et al.*, 2013).

Supplement

Table S1 Clinical and demographic details of the study sample.

ID (sex, age in yrs.)	Site of amputation	Handedness prior to amputation	Time since amputation (yrs.)	Reason for amputation	Phantom pain frequency	MPI phantom pain	Prosthesis type	Telescoping (%)*	Residual limb length (%)	MPI stump pain
A1 (M, 51)	Left	Right	33	Trauma	several times a week	3.00	Cosmetic	70	70	3.00
A2 (M, 53)	Right	Right	36	Tumor	several times a month	1.00	Myoelectric	55	26	0.67
A3 (F, 42)	Left	Right	17	Vascular	permanently	1.33	No	45	42	1.33
A4 (M, 53)	Right	Right	32	Trauma	several times a day	4.00	No	20	20	0.33
A5 (F, 23)	Left	unknown	21	Trauma	no	0.00	No	100	70	0.00
A6 (M, 36)	Left	Right	4	Trauma	several times a day	4.33	No	38	25	0.00

A7 (F, 57)	Left	Right	30	Tumor	< once a month	2.00	No	0	0	0.00
A8 (M, 60)	Left	Right	23	Trauma	permanently	2.00	No	59	24	0.00
A9 (F, 28)	Right	Right	11	Trauma	permanently	2.33	No	100	36	2.00
A10 (F, 54)	Right	Right	31	Trauma	several times a week	3.67	Myoelectric	0	70	2.67
A11 (M, 47)	Left	Right	32	Tumor	no	0.00	Myoelectric	68	25	0.33
A12 (M, 70)	Left	Right	67	Trauma	no	0.00	Cosmetic	95	43	0.00
M/SD=47.83/13.52	4 R	11 R	28.08/15.04			1.97/1.56	5x Prosthesis	54.17/35.31	37.58/22.48	0.86/1.11

*Length of residual limb is given as a percentage of the length of the intact limb as measured from caput humeri to tip of middle finger. M=male; F=female

Table S2 Regions of interest used in the regressive psychophysiological interaction analysis.

fROI (BA6/44/45) (L)	M1 (BA4a) (L/R)	Hippocampus formation (L/R)[*]
Precentral gyrus (R)	M1 (BA4p) (L/R)	Nucleus accumbens (L/R)
aIPS (hIP1) (L/R)	SI (BA1) (L/R)	Amygdala formation (L/R)[*]
aIPS (hIP2) (L/R)	SI (BA2) (L/R)	Caudate nucleus (L/R)
aIPS (hIP3) (L/R)	SI (BA3a) (L/R)	Pallidum (L/R)
BA44 (R)	SI (BA3b) (L/R)	Putamen (L/R)
BA45 (R)	**SPL (5Ci) (L/R)**	Thalamus (L/R)
IPL (PFcm) (L/R)	**SPL (5L) (L/R)**	Primary auditory cortex (L/R)[*]
IPL (PF) (L/R)	**SPL (5M) (L/R)**	S2(OP1) (L/R)
IPL (PFm) (L/R)	**SPL (7A) (L/R)**	S2 (OP2) (L/R)
IPL (PFop) (L/R)	**SPL (7M) (L/R)**	S2 (OP3) (L/R)
IPL (PFt) (L/R)	**SPL (7PC) (L/R)**	S2 (OP4) (L/R)
IPL (Pga) (L/R)	**SPL (7P) (L/R)**	
IPL (Pgp) (L/R)	BA17 (L/R)	
Insula (Id1) (L/R)	BA18 (L/R)	
Insula (Ig1) (L/R)	V3V (L/R)	
Insula (Ig2) (L/R)	V4 (L/R)	
Insula (Ig2) (L/R)	V5 (L/R)	

Regions that were modelled as seeds are written with bold letters. [*]Region consists of fusion of the following sub-regions derived from the Juelich-Histological atlas: Amygdala (centromedial, laterobasal and superficial group); Hippocampus formation (cornu ammonis, dentate, subiculum, enthorhinal); Primary auditory cortex (TE 1.0, 1.1 and 1.2).

Table S3. Perceptual qualities and intensities reported by the yoked controls subsequent to the stimulation of body sites homologous to the amputees in the MRI.

Healthy control matched to:	Matched stimulation method	Intensity at the stimulated site	Valence at the stimulated site	Sensations remote from the stimulated site
A1	electric	5	-2	no
A2	pneumatic	8	0	no
A3	pneumatic	10	0	no
A4	electric	1	0	no
A5	electric	10	-2	no
A6	pneumatic	5	0	no
A7	pneumatic	2	0	no
A8	pneumatic	8	0	no
A9	pneumatic	6	2	no
A10	pneumatic	6	0	no
A11	pneumatic	7	0	no
A12	pneumatic	5	-4	no
Mean/Median		6.08/6	-0.5/0	
±SD		2.78	1.51	

Intensities and valence were assessed using a numerical rating scale. Intensity ratings ranged from 0 '*no sensation*' to 10 '*most intense sensation*' and valence ratings ranged from -10 '*very unpleasant*' to 10 '*very pleasant*'.

Table S4 Peak voxel coordinates of brain regions showing mean responses during the evoked phantom sensations and control site condition in the amputees.

Region	MNI [mm] x	y	z	z-score	cluster extent [voxel]	Region	MNI [mm] x	y	z	z-score	cluster extent [voxel]
evoked phantom sensations						**control site**					
Central operculum (OP1)	-58	-20	20	5.17	5480	Parietal operculum (OP1)	56	-28	18	4.26	728
Precentral gyrus	-60	2	2	4.5			42	-32	18	4.18	
Central operculum (OP1)	-56	-16	12	4.48			56	-20	16	4.12	
Postcentral gyrus	-64	-16	14	4.44		Posterior cingulum	-2	-30	32	3.36	596
Parietal operculum (OP4)	-66	-10	6	4.38			2	-24	36	3.33	
Postcentral gyrus	-66	-22	22	4.12			10	-30	36	3.28	
Parietal operculum (OP4)	60	-26	22	4.55	2169	Paracingulum	-4	36	36	3.71	433
	52	-12	12	4.48			2	38	34	3.44	
Parietal operculum (OP1)	48	-30	22	4.04		Superior frontal gyrus	-4	28	48	3.38	

Region	x	y	z	z-stat	size	Region	x	y	z	z-stat	size
	54	-24	16	3.98		Middle frontal gyrus	-38	12	50	3.63	376
Central operculum (OP4)	44	-12	16	3.96			-48	26	38	3.45	
	56	-6	6	3.91			-50	26	34	3.44	
control site						Precuneus	-2	-74	44	3.53	368
Postcentral gyrus	-62	-22	20	4.92	3312		4	-74	40	3.49	
Precentral gyrus	-58	4	4	4.01			-6	-74	42	3.35	
Parietal operculum (OP1)	-48	-24	20	3.88		Frontal pole	44	56	6	3.7	353
Parietal operculum (OP1)	-52	-24	22	3.86			44	58	2	3.32	
Central operculum (OP4)	-56	0	4	3.86			42	46	24	3.31	
Postcentral gyrus	-52	-16	22	3.81		Precentral gyrus	62	6	6	4.08	300
							58	4	10	3.57	

Clusters of significant brain responses were determined using a $z > 2.3$ threshold and a corrected cluster threshold of $p=0.05$ assuming a Gaussian random field for the z-statistics.
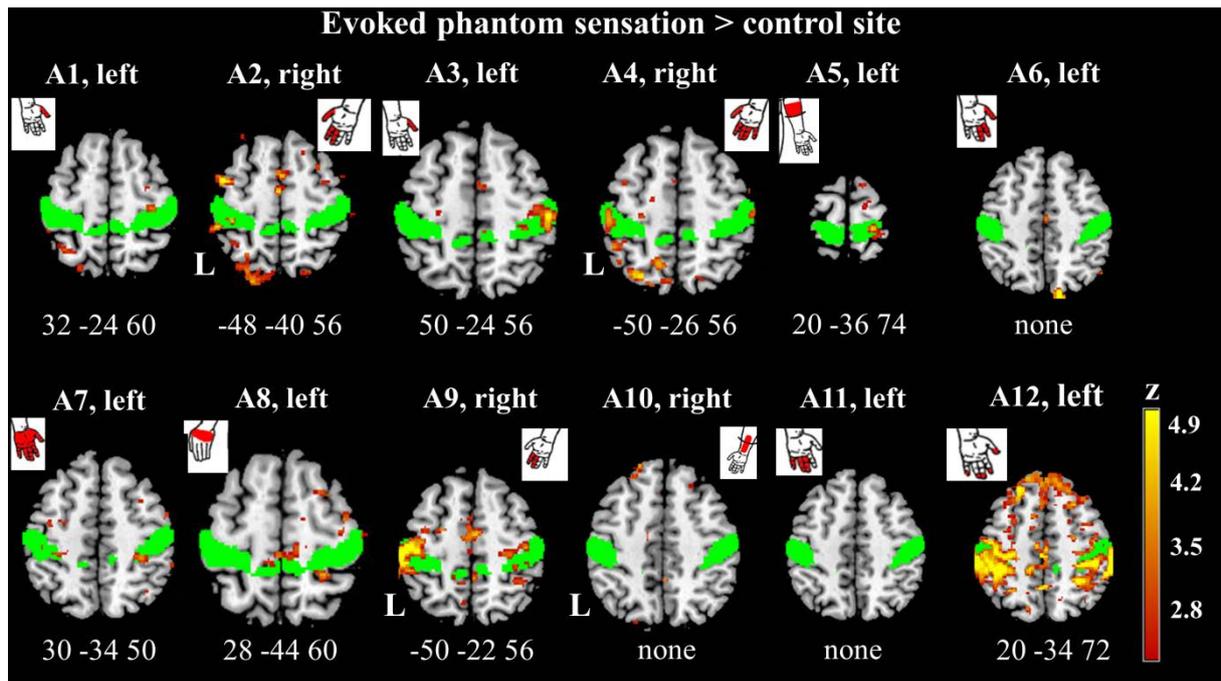
Figure S5 Brain activation related to evoked phantom sensations in SI derived from the evoked phantom sensations > control site contrast. The green shaded area shows a probabilistic mask of the postcentral gyrus[*]. Clusters and peak voxel coordinates are shown for each amputee (A1-A12). The amputees A2, A4, A9, and A10 were right-sided amputees with expected left-hemispheric (L) SI-representation of the phantom limb. Functional images were derived from the subject-wise evoked phantom sensations > control site contrasts.

Images were created at a *z* > 2.3 and cluster-corrected p=0.05 threshold and overlaid on the MNI template as provided by mricron. [*]Harvard-Oxford Atlas, 30% probability threshold.

References

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007). Non-linear registration aka Spatial normalisation FMRIB Technial Report TR07JA2, (June).

Andoh, J., Diers, M., Milde, C., Köppe, C., Kleinböhl, D., & Flor, H. (2017). Neural correlates of evoked phantom limb sensations. *Biological Psychology*. doi:10.1016/j.biopsycho.2017.04.009

Apps, M. A. J., Tajadura-Jiménez, A., Sereno, M., Blanke, O., & Tsakiris, M. (2015). Plasticity in unimodal and multimodal brain areas reflects multisensory changes in self-face identification. *Cerebral Cortex (New York, N.Y. : 1991)*, *25*(1), 46–55. doi:10.1093/cercor/bht199

Baliki, M. N., Geha, P. Y., & Apkarian, A. V. (2009). Parsing pain perception between nociceptive representation and magnitude estimation. *Journal of Neurophysiology*, *101*(2), 875–87. doi:10.1152/jn.91100.2008

Bates, D., Maechler, M., Bolker, B., & Walker, S. (2014). lme4: Linear mixed-effects models using Eigen and S4. R package version 1.1–7.

Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2003). General multilevel linear modeling for group analysis in FMRI. *NeuroImage*, *20*(2), 1052–1063. doi:10.1016/S1053-8119(03)00435-X

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. doi:10.1016/j.neuroimage.2007.04.042

Bekrater-Bodmann, R., Schredl, M., Diers, M., Reinhard, I., Foell, J., Trojan, J., … Flor, H. (2015). Post-amputation pain is associated with the recall of an impaired body representation in dreams-results from a nation-wide survey on limb amputees. *PloS One*, *10*(3), e0119552. doi:10.1371/journal.pone.0119552

Björkman, A., Weibull, A., Olsrud, J., Ehrsson, H. H., Rosén, B., & Björkman-Burtscher, I. M. (2012). Phantom digit somatotopy: a functional magnetic resonance imaging study in forearm amputees. *The European Journal of Neuroscience*, *36*(1), 2098–106. doi:10.1111/j.1460-9568.2012.08099.x

Blanke, O., Slater, M., & Serino, A. (2015). Behavioral, Neural, & Computational Principles of Bodily Self-Consciousness. *Neuron*, *88*(1), 145–166.

doi:10.1016/j.neuron.2015.09.029

Bolognini, N., Olgiati, E., Maravita, A., Ferraro, F., & Fregni, F. (2013). Motor and parietal cortex stimulation for phantom limb pain and sensations. *Pain*, *154*(8), 1274–1280. doi:10.1016/j.pain.2013.03.040

Bolognini, N., Spandri, V., Ferraro, F., Salmaggi, A., Molinari, A. C. L., Fregni, F., … Garcia-Larrea, L. (2015). Immediate and Sustained Effects of 5-Day Transcranial Direct Current Stimulation of the Motor Cortex in Phantom Limb Pain. *The Journal of Pain : Official Journal of the American Pain Society*, *16*(7), 657–65. doi:10.1016/j.jpain.2015.03.013

Borsook, D., Becerra, L., Fishman, S., Edwards, A., Jennings, C. L., Stojanovic, M., … Breiter, H. (1998). Acute plasticity in the human somatosensory cortex following amputation. *Neuroreport*, *9*(6), 1013–7.

Botvinick, M., & Cohen, J. (1998). Rubber hands "feel" touch that eyes see. *Nature*, *391*(6669), 756–756. doi:10.1038/35784

Brugger, P., Kollias, S. S., Müri, R. M., Crelier, G., Hepp-Reymond, M. C., Regard, M., … Regard, M. (2000). Beyond re-membering: phantom sensations of congenitally absent limbs. *Proc Natl Acad Sci USA*, *97*(11), 6167–6172. doi:10.1073/pnas.100510697

Cronholm, B. (1951). Phantom limbs in amputees; a study of changes in the integration of centripetal impulses with special reference to referred sensations. *Acta Psychiatrica et Neurologica Scandinavica. Supplementum*, *72*, 1–310.

Davis, K. D., Kucyi, A., & Moayedi, M. (2015). The pain switch. *PAIN*, *156*(11), 2164–2166. doi:10.1097/j.pain.0000000000000303

Dietrich, C., Walter-Walsh, K., Preissler, S., Hofmann, G. O., Witte, O. W., Miltner, W. H. R., & Weiss, T. (2012). Sensory feedback prosthesis reduces phantom limb pain: proof of a principle. *Neuroscience Letters*, *507*(2), 97–100. doi:10.1016/j.neulet.2011.10.068

Ehrsson, H., Holmes, N. P., & Passingham, R. E. (2005). Touching a Rubber Hand: Feeling of Body Ownership Is Associated with Activity in Multisensory Brain Areas. *Journal of Neuroscience*, *25*(45), 10564–10573. doi:10.1523/JNEUROSCI.0800-05.2005

Ehrsson, H., Spence, C., & Passingham, R. E. (2004). That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. *Science (New York, N.Y.), 305*(5685), 875–7. doi:10.1126/science.1097011

Eickhoff, S. B., Paus, T., Caspers, S., Grosbras, M. H., Evans, A. C., Zilles, K., & Amunts, K. (2007). Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. *NeuroImage, 36,* 511–521. doi:10.1016/j.neuroimage.2007.03.060

Fink, G. R., Marshall, J. C., Halligan, P. W., Frith, C. D., Driver, J., Frackowiak, R. S., & Dolan, R. J. (1999). The neural consequences of conflict between intention and the senses. *Brain : A Journal of Neurology, 122 (Pt 3,* 497–512.

Finnerup, N., Nikolajsen, L., & Jensen, T. S. (2012). Are we neglecting spinal reorganization following nerve damage? *Pain, 153*(2), 269–72. doi:10.1016/j.pain.2011.10.030

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

Flor, H., Mu, C. A. W., Karl, A., Denke, C., Gru, S., Kurth, R., & Taub, E. (2000). A neural substrate for nonpainful phantom limb phenomena. *Neuroreport, 11*(7), 1407–1411.

Flor, H., Rudy, T. E., Birbaumer, N., Streit, B., & Schugens, M. M. (1990). [The applicability of the West Haven-Yale multidimensional pain inventory in German-speaking countries. Data on the reliability and validity of the MPI-D.]. *Schmerz (Berlin, Germany), 4*(2), 82–87. doi:10.1007/BF02527839

Foell, J., Bekrater-Bodmann, R., Diers, M., & Flor, H. (2014). Mirror therapy for phantom limb pain: Brain changes and the role of body representation. *European Journal of Pain (London, England), 18*(5), 1–11. doi:10.1002/j.1532-2149.2013.00433.x

Friston, K. J., Penny, W. D., & Glaser, D. E. (2005). Conjunction revisited. *NeuroImage, 25*(3), 661–7. doi:10.1016/j.neuroimage.2005.01.013

Gentile, G., Guterstam, A., Brozzoli, C., & Ehrsson, H. H. (2013). Disintegration of multisensory signals from the real hand reduces default limb self-attribution: an fMRI study. *The Journal of Neuroscience : The Official Journal of the Society for*

Neuroscience, 33(33), 13350–66. doi:10.1523/JNEUROSCI.1363-13.2013

Giummarra, M. J., Georgiou-Karistianis, N., Nicholls, M. E. R., Gibson, S. J., Chou, M., & Bradshaw, J. L. (2011). The menacing phantom: what pulls the trigger? *European Journal of Pain (London, England), 15*(7), 691.e1-8. doi:10.1016/j.ejpain.2011.01.005

Giummarra, M. J., & Moseley, G. (2011). Phantom limb pain and bodily awareness: current concepts and future directions. *Current Opinion in Anaesthesiology, 24*(5), 524–31. doi:10.1097/ACO.0b013e32834a105f

Grivaz, P., Blanke, O., & Serino, A. (2017). Common and distinct brain regions processing multisensory bodily signals for peripersonal space and body ownership. *NeuroImage, 147*(iii), 602–618. doi:10.1016/j.neuroimage.2016.12.052

Grüsser, S. M., Mühlnickel, W., Schaefer, M., Villringer, K., Christmann, C., Koeppe, C., & Flor, H. (2004). Remote activation of referred phantom sensation and cortical reorganization in human upper extremity amputees. *Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation Cérébrale, 154*(1), 97–102. doi:10.1007/s00221-003-1649-4

Grüsser, S. M., Winter, C., Mühlnickel, W., Denke, C., Karl, A., Villringer, K., & Flor, H. (2001). The relationship of perceptual phenomena and cortical reorganization in upper extremity amputees. *Neuroscience, 102*(2), 263–72.

Guterstam, A., Gentile, G., & Ehrsson, H. H. (2013). The invisible hand illusion: multisensory integration leads to the embodiment of a discrete volume of empty space. *Journal of Cognitive Neuroscience, 25*(7), 1078–99. doi:10.1162/jocn_a_00393

Hunter, J., Katz, J., & Davis, K. (2003). The effect of tactile and visual sensory inputs on phantom limb awareness. *Brain, 126*(Pt 3), 579–589. doi:10.1093/brain/awg054

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage, 17*(2), 825–841. doi:10.1006/nimg.2002.1132

Jensen, T. S., Krebs, B., Nielsen, J., & Rasmussen, P. (1984). Non-painful phantom limb phenomena in amputees: incidence, clinical characteristics and temporal

course. *Acta Neurologica Scandinavica, 70*(6), 407–14.

Jensen, T. S., Krebs, B., Nielsen, J., & Rasmussen, P. (1985). Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation limb pain. *Pain, 21*(3), 267–78.

Kerns, R. D., Turk, D. C., & Rudy, T. E. (1985). The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). *Pain, 23*(4), 345–356.

Knecht, S., Henningsen, H., Elbert, T., Flor, H., Höhling, C., Pantev, C., & Taub, E. (1996). Reorganizational and perceptional changes after amputation. *Brain : A Journal of Neurology, 119 (4)*, 1213–9.

Knecht, S., Sörös, P., Gürtler, S., Imai, T., Ringelstein, E. B., & Henningsen, H. (1998). Phantom sensations following acute pain. *Pain, 77*(2), 209–13.

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2014). *lmerTest: Tests for random and fixed effects for linear mixed effect models (lmer objects of lme4 package).*

Lotze, M., Grodd, W., Birbaumer, N., Erb, M., Huse, E., & Flor, H. (1999). Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? *Nature Neuroscience, 2*(6), 501–2. doi:10.1038/9145

Makin, T. R., Holmes, N. P., & Zohary, E. (2007). Is that near my hand? Multisensory representation of peripersonal space in human intraparietal sulcus. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 27*(4), 731–740. doi:10.1523/JNEUROSCI.3653-06.2007

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches. *NeuroImage, 61*(4), 1277–1286. doi:10.1016/j.neuroimage.2012.03.068

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

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113.

Pons, T. P., Garraghty, P. E., & Mishkin, M. (1988). Lesion-induced plasticity in the second somatosensory cortex of adult macaques. *Proceedings of the National*

Academy of Sciences of the United States of America, *85*(14), 5279–81.

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

Preißler, S., Dietrich, C., Blume, K. R., Hofmann, G. O., Miltner, W. H. R., & Weiss, T. (2013). Plasticity in the Visual System is Associated with Prosthesis Use in Phantom Limb Pain. *Frontiers in Human Neuroscience*, *7*(June), 311. doi:10.3389/fnhum.2013.00311

R Development Core Team. (2015). A language and environment for statistical computing. Goettingen (Germany): R Foundation for statistical computing.

Ramachandran, V., Stewart, M., & Rogers-Ramachandran, D. (1992). Perceptual Correlates of Massive Cortical Reorganization. *Neuroreport*, *3*(7), 583–586. doi:10.1097/00001756-199207000-00009

Rosén, B., Ehrsson, H. H., Antfolk, C., Cipriani, C., Sebelius, F., & Lundborg, G. (2009). Referral of sensation to an advanced humanoid robotic hand prosthesis. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery / Nordisk Plastikkirurgisk Forening [and] Nordisk Klubb for Handkirurgi*, *43*(5), 260–6. doi:10.3109/02844310903113107

Schady, W., Braune, S., Watson, S., Torebjörk, H. E., & Schmidt, R. (1994). Responsiveness of the somatosensory system after nerve injury and amputation in the human hand. *Annals of Neurology*, *36*(1), 68–75. doi:10.1002/ana.410360114

Schmalzl, L., Kalckert, A., Ragnö, C., & Ehrsson, H. H. (2013). Neural correlates of the rubber hand illusion in amputees: A report of two cases. *Neurocase*, *20*(4), 407–420. doi:10.1080/13554794.2013.791861

Schmalzl, L., Kalckert, A., Ragnö, C., & Ehrsson, H. H. (2014). Neural correlates of the rubber hand illusion in amputees: a report of two cases. *Neurocase*, *20*(4), 407–20. doi:10.1080/13554794.2013.791861

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–55. doi:10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J.,

Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23 Suppl 1*, 208–219. doi:10.1016/j.neuroimage.2004.07.051

Tsakiris, M. (2010). My body in the brain: a neurocognitive model of body-ownership. *Neuropsychologia*, *48*(3), 703–12. doi:10.1016/j.neuropsychologia.2009.09.034

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connectivity*, *2*(3), 125–141. doi:10.1089/brain.2012.0073

Wickham, H. (2009). *ggplot2: elegant graphics for data analysis.* New York: Springer Science & Business Media.

Wienbruch, C., Candia, V., Svensson, J., Kleiser, R., & Kollias, S. S. (2006). A portable and low-cost fMRI compatible pneumatic system for the investigation of the somatosensory system in clinical and research environments. *Neuroscience Letters*, *398*(3), 183–188. doi:10.1016/j.neulet.2006.01.025

Winter, C., Fritsche, K., Karl, A., Huse, E., Labig, W., Grusser, S. M., & Flor, H. (2001). [The phantom and stump phenomena interview (PSPI)]. *Schmerz*, *15*(3), 172–178. Journal Article.

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *NeuroImage*, *14*(6), 1370–86. doi:10.1006/nimg.2001.0931

Yoo, S.-S., Freeman, C. A. D. K., McCarthy, J. J., & Jolesz, F. A. (2003). Neural substrates of tactile imagery : a functional MRI study, *14*(4). doi:10.1097/01.wnr.0000063506.18654.91

4 GENERAL DISCUSSION

4.1 Main Findings

The aim of the present thesis was to provide novel insights into the psychobiological mechanisms of experimentally altered body perception in healthy subjects and amputees. A better understanding of the psychobiological mechanisms of altered body perception could help to develop new approaches to relieve pain and disability in otherwise often difficult to treat conditions related to altered bod representation such as phantom limb pain (Deconinck et al., 2014; Foell et al., 2014; Rousseaux et al., 2014).

Study 1

Study 1 investigated the self-reported capacity for mirror illusion and the neural correlates of the novel mirror glasses in comparison to the well-established mirror box in healthy volunteers. Both mirror devices differ conceptually: the mirror glasses visually occlude the actually moving limb (Walsh and Bannister, 2010), while the mirror box enables view on both limbs that appear to move in synchrony (Ramachandran and Rogers-Ramachandran, 1996).

In accordance with our hypothesis, functional imaging showed a recruitment of the primary sensorimotor representation of the non-mirrored limb in both mirror conditions (**H2**). Replicating previous studies using mirror visual feedback in healthy subjects (Matthys et al. 2009; Deconinck et al. 2014), we found significant activation in brain regions typically involved in mirror illusions in both mirror tasks, validating the role of the mirror glasses for mirror therapy (**H3**) (Matthys et al., 2009). These brain regions encompassed the premotor, superior parietal, and lateral occipital cortices, the supplementary motor area and the ipsilateral cerebellum.

Contrary to our hypothesis, the self-reported mirror illusion capacity did not significantly differ between the mirror glasses and the mirror box condition, as indicated by ratings on the vividness and intensity of the mirror illusion (**H1**). The lack of significant differences cannot be explained by floor effects. The ratings on mirror illusions were comparable to former studies using similar items with moderate illusion intensities (Diers et al., 2015, 2010). We also did not find significant differences in brain activation in the primary sensorimotor cortex corresponding to the non-mirrored

limb between both mirror conditions (**H4**). Notably, any tilt of the mirror glasses by head-movements causes substantial rotation of the mirrored body parts as compared to only slight displacements caused by head movements with the mirror box (Walsh and Bannister, 2010). In relation to the four constraints determining bodily-self-consciousness as proposed by Blanke et al. (2015) (section 1.1), these rotations of mirrored body parts cause biophysically inconsistent positions of the virtual recreation of the moving limb. According to the proprioceptive constraint, the hand has to be presented in a biophysically plausible position. Due to head-movements however, the hand was temporally seen in biophysically implausible angles with the mirror glasses, which might have diminished the mirror illusions. Hadoush et al. (2013) used a different experimental setup to occlude the view on the actual moving limb that was not sensitive to head movements, which might explain higher self-reported mirror illusion capacity in that study. Furthermore, the authors used different items to assess the strength of the mirror illusion and used different task instructions. Noteworthy, Hadoush et al. (2013) instructed the subjects to perform motor imagery during the mirror tasks, while we used the standard instructions as originally used by Ramachandran and Rogers-Ramachandran (1996). The combination of mirror therapy with specific instructions or task using involving motor imagery has been shown to lead to higher self-reported mirror illusions and pain reduction (McCabe, Haigh, & Blake, 2008; Moseley, 2006).

It has been discussed that the non-mirrored limb representation is recruited via contralateral projections arising from the motor representation of the moving (intact) limb (Avanzino et al., 2014; Ezendam, Bongers, & Jannink, 2009; Nojima et al., 2012). Contrary to our hypotheses, we found a significant increase in interhemispheric communication between sensorimotor hand representations only in the mirror glasses condition, while it was absent in the mirror box condition (**H5**). Until now, the functional connectivity during mirror visual feedback has been rarely addressed (Deconinck et al. 2014). Thus, knowledge about functional integration and communication between brain regions specific for mirror visual feedback is lacking. Moreover, the hypothesis on interhemispheric communication potentially driving activity in the non-mirrored limb representation can only be answered using connectivity studies or neuromodulation techniques causally manipulating neural activity in stimulated cortical regions (Läppchen et al., 2012).

In summary, we found that the mirror glasses, which systematically exclude the view on the actually moving limb, lead to comparable mirror illusions and similar brain activation. The potentially distracting effect of seeing the moving limb in addition to the visual recreation did not diminish the quality of mirror illusions, however, head-movements generating dynamic visuo-proprioceptive mismatches might be confounding. Our results suggest different neural circuitry for both types of mirror illusions and tasks contexts.

Study 2

Study 2 investigated the neural circuitry of non-painful phantom sensations in unilateral upper-limb amputees elicited remote from the residual limb. In line with our hypothesis, the evoked phantom sensations could be elicited at body sites that cannot readily be explained by topographic reorganization in SI (**H1**). Besides elicitation sites for non-painful phantom sensations at the residual limb, the ipsilateral face and trunk – that are in accordance with the topographical reorganization hypothesis for phantom phenomena (Ramachandran et al., 1992) – we also found elicitation sites at the leg or at body sites contralateral to the amputation. Thus, we replicated previous studies, showing that phantom sensations could be elicited at body sites that cannot readily be explained by topographic reorganization in SI (Borsook et al., 1998; Grüsser et al., 2004; Knecht et al., 1998). In line with our hypotheses (**H2**), brain activation specific for evoked phantom sensations was found in a widespread fronto-parietal network, including areas that have been shown to be important for body illusions or have been identified in neurological conditions linked to altered body perception including the insula, BA44/45, and premotor and posterior parietal regions (Blanke et al., 2015; Grivaz et al., 2017). In line with our hypothesis (**H3**), we found significant activation in the secondary somatosensory cortices in the evoked phantom sensation versus control conditions. A significant activation of the secondary somatosensory cortex was assumed since the secondary somatosensory cortex shows receptive field spanning multiple body regions such as trunk and upper-limb as well as inter-limb receptive fields (Taoka et al., 2016). Thus, the topography of the body maps in secondary somatosensory cortex could better explain phantom sensations elicited remote from the deafferentation line. We found elicitation sites at the ipsi- and contralateral leg in four amputees and trunk elicitation sites in half of the

amputees, which is might be explained with body maps in the secondary somatosensory cortex.

In line with our hypothesis **(H4),** we found that non-painful evoked phantom sensations are related to significantly increased connectivity within a fronto-parietal network. Specifically, we found increased coupling between the functionally defined ventral frontal cortex and multiple posterior parietal regions as well as increased inter and intraparietal coupling. Recently, a study found increased task-dependent connectivity between left-hemispheric ventral frontal and posterior parietal regions in a modified version of the rubber hand illusion. The authors induced the experience of ownership and referring of touch to a portion of empty space – similar to the perception of supernumerary phantom limbs or the perception of non-painful phantoms.

To summarize, our findings provide evidence linking evoked phantom sensations to neural circuitry discussed to be important for altered body perception in body illusions or in neurological syndromes (section 1.1). In sum, both studies associate illusory body perception with brain activity in regions discussed to be important for body illusions. Despite of conceptual differences between mirror illusions and evoked phantom sensations and different participant groups in both tasks, similar brain regions including the superior parietal lobe or premotor regions were involved in both studies. Indeed a recent meta-analysis revealed common co-activations in a widespread fronto-parietal network to be commonly involved in altered body perception across multiple task contexts (Grivaz et al., 2017).

4.2 Conceptual communalities and differences between the studies

This section discusses conceptual differences and commonalities between both studies referring to the model of bodily-self-consciousness proposed by Blanke et al. (2015) and the neurocognitive model of body-ownership proposed by Tsakiris (2010) (see section 1.1).

Study 1 constitutes a typical experimental setup to alter body representations via ambiguous multisensory input with bodily-signals as described in Blanke et al. (2015) involving exteroceptive (visual recreation of a moving limb) and bodily signals (arm-related proprioception). Hence, the mirror illusions in Study 1 were expected to be determined by the four constraints on bodily-self-consciousness as proposed by

Blanke et al. (2015) (section 1.1 and Figure 1). The *embodiment constraint* states that a prolonged period of spatiotemporally congruent stimulation can lead to embodiment and adaption of the peripersonal space. In line with that, it is assumed that prolonged induction of the mirror illusion give rise to a temporally-graded adaption of the spatially incongruent position between the resting arm and the visual recreation of the moving limb by reshaping the peripersonal space. The *proprioceptive constraint* states that the (artificial) body part must be presented in a biophysically plausible manner and the *body-related visual information constraint* states that the (artificial) body part shall resemble the human body. In line with that, the visual recreation of a moving limb was presented in a biophysically plausible manner and resembles the human body in both mirror conditions. The *peripersonal constraint* states that the (artificial) body part shall be presented within the perispersonal space of the subject. The 'virtual limb' was presented within the peripersonal space of the hidden arm. In principle the peripersonal space could be highly discrepant and remote from the physical body such as in full-body illusion referring to prolonged spatiotemporal coherent stimulation, underlining the importance of the embodiment constraint.

Study 2 in contrast did neither involve motor execution nor visual-feedback as a constitutive component of the illusory perception. Simple unisensory stimulation was used to induce a perception paradoxically allocated to the phantom limb. In contrast to the studies reported by Blanke et al. (2015), Study 2 involves illusory body perception in a clinical population (amputees) and bodily-signals were not integrated with visual input. Tsakiris (2010) suggested that exteroceptive stimuli, such as visual, further interact with a (stimulus-independent) *internal model of the body* that also determines the experiences with body illusions. Noteworthy, in neurological patients with distorted body perception this internal body model is already altered (de Preester & Tsakiris, 2009). The importance of assuming internal (stimulus-independent) body representations becomes evident in amputees with spontaneous (stimulus-independent) phantom phenomena. In amputees with evoked phantom sensations the perception of the phantom limb is in general also present in the absence of an identifiable external stimulus (Hunter, Katz, & Davis, 2005). Thus, in comparison to the mirror illusions used in Study 1 and the other body illusions described in sections 1.1 and 1.3, the unimodal elicitation of evoked phantom sensations in Study 2 does

not necessarily involve an update of the representation of the body by prolonged stimulation reshaping the peripersonal space. In our sample, nonpainful phantom sensations could be evoked with a stimulation-related on and offset. The dispensability of a prolonged stimulation periods to induce the perception of evoked phantom sensations might indicate that evoked phantom sensations could be allocated to an already existing internal model of a phantom, without having to reshape the peripersonal space. To conclude, it seems reasonable to assume that evoked phantom sensations are linked to a modulation of stimulus-independent internal models of the body in the brain.

4.3 Clinical importance of the present results

Multiple lines of evidence point towards a mechanistic link between altered body perception and chronic pain: Multimodal body illusion setups, such as the mirror illusions, have been shown to be efficient in reducing pain and disability by normalizing body perception (Bekrater-Bodmann et al., 2011; Christ & Reiner, 2014; Longo, Betti, Aglioti, & Haggard, 2009) and to be further accompanied by a reversal of maladaptive cortical alterations (Foell et al., 2014).

In 60-80% of the cases amputees report to have phantom pain (Carlen et al., 1978; Kooijman et al., 2000). Phantom pain shows a high degree of chronicity and successful treatment approaches are rare. The pathophysiology and etiology of phantom pain remains unknown (Weeks et al., 2010). In addition to phantom pain, almost all amputees also experience non-painful phantom sensations such as the telescoping phenomenon or evoked phantom sensations (Sherman, 1997). Recent studies using neuromodulation techniques, indicate that different neural substrates are causally linked to painful versus non-painful phantom phenomena (Bolognini et al., 2015, 2013).

Mirror therapy has been shown to be successful in various pain and disability conditions including phantom limb pain (Foell et al., 2014), complex regional pain syndrome (McCabe et al., 2003), somatoparaphrenia (Fotopoulou et al., 2011) or motor rehabilitation following stroke (Invernizzi et al., 2012), although long-term controlled studies are lacking. The mirror box, however, is constrained by its size and weight, which reduces the degrees of freedom for possible movements in front of the mirror. The mirror glasses are smaller in size and weight than the mirror box (Walsh

& Bannister, 2010). Virtual reality has been used to overcome the shortages of the classical mirror box (Diers et al., 2015; Murray et al., 2007). Compared to virtual-reality systems, mirror glasses are cheaper and deliver a more realistic image of the mirrored limb. The visual resemblance with the human body has been shown to be an important factor for body illusions (Tsakiris, Schuetz-Bosbach, & Gallagher, 2007) and is also conceptualized in the body-related visual information constraint of Blanke et al. (2015) stating that the induction and strength of the body illusion strongly depends on the visual resembles between the object used in the illusion and the human body (section 1.1). Thus, the mirror glasses might be more attractive for healthcare providers and more appropriate in research paradigms involving functional imaging. Study 2 emphasizes important contextual differences between mirror visual feedback paradigms, which might affect the therapeutic efficiency of the intervention. Both mirror conditions varied in whether both hands appeared to move in synchrony or if only the mirror image of the moving limb was in view. We did not find significant differences in the self-reported mirror illusion capacity; however, we found significant differences in the functional connectivity underlying both mirror conditions. These differences in neural circuitry underlying both mirror tasks emphasize the role of investigating the interplay between contextual factors and neural circuitry of mirror illusions that determines therapeutic success.

Knowledge about contextual factors and neural mechanisms of non-painful phantom phenomena in amputees might help to develop novel treatment approaches based on multisensory integration with bodily signals (Blanke et al., 2015). For example, it has been shown that the degree of telescoping was associated with phantom pain alleviation and accompanying sensorimotor plasticity in mirror therapy, indicating the importance of a deeper understanding of non-painful phantom phenomena in the context of nonpharmacological phantom pain treatments (Foell et al., 2014). As discussed in section 1.2, there is ample evidence that painful phantom phenomena are linked to topographic reorganization in primary sensorimotor cortices, while non-painful phantom phenomena have been discussed to be dependent on more associative brain regions such as the posterior parietal cortex (Grüsser et al., 2001, 2004).

Knecht et al (1996) found a significant positive correlation between cortical reorganization in SI and the number of body sites, from which painful phantom

sensations can be elicited by painful stimulation. However, Knecht et al (1996) did not report on the type of evoked phantom sensations (painful, non-painful). Grüsser et al. (2001) found a significant positive correlation between cortical reorganization in SI and the painful phantom sensations elicited by painful stimulation and habitual phantom pain, but no such relationship for non-painful phantom sensations or stump pain. Study 2 provides evidence that non-painful phantom phenomena depend on a widespread network of fronto-parietal regions capable of integrating multisensory input and to form coherent perception of the body. The interplay between painful- and non-painful phantom phenomena and its modification within multimodal body illusions is not well understood (Bekrater-Bodmann et al., 2011). By making use of evoked phantom sensations, recent research on body illusions in amputees found promising approaches aiming at increasing the sense of ownership and agency for the prosthesis (Ehrsson et al., 2008; Rosén et al., 2009) or to successfully apply a 'movement-independent' version of mirror training to formerly mirror visual feedback-resistant phantom pain patients (Schmalzl, Ragnö, & Ehrsson, 2013). The use of a prosthesis, especially of a functional prosthesis, such as a myoelectric prosthesis, might be beneficial for phantom pain relief and is associated with a reduction of cortical reorganization (Lotze et al. 1999). But, many amputees have problems accepting a prosthesis or to use it on a regular basis, for example, due to the missing controllability over the prosthesis (Ehrsson et al., 2008). Somatosensory feedback is relevant for the embodiment of prosthesis and can optimize motor control and learning with the prosthesis, thus increasing acceptance and usage of the prosthesis (Dietrich et al., 2012; Weiss, Miltner, Adler, Brückner, & Taub, 1999). Ehrsson et al. (2008) induced the rubber hand illusion in subjects by simultaneous visuo-tactile stimulation of a fake limb and residual limb sites eliciting localized evoked phantom sensations corresponding to the visual stimulation on the rubber hand in most of the amputees. Rosén et al. (2009) transferred the rubber hand illusion to an artificial robotic prosthesis offering new avenues in the field of neuro-prosthetics. Schmalzl, Ragnö, et al. (2013) developed a visuo-tactile version of mirror therapy without movements by synchronously stroking residual limb sites eliciting evoked phantom sensations and visually stroking corresponding sites on the intact hand seen in the mirror. The authors reported reduced phantom pain in patients who were resistant to conventional mirror therapy due to mirror-movement-induced painful spasms in the

phantom limb. Combining the elicitation of evoked phantom sensations with exteroceptive cues and bodily-signals might provide new avenues to reshape maladaptive neural and mental representations of the body, such as painfully clenched phantoms (Rosén et al., 2009; Schmalzl, Kalckert, Ragnö, & Ehrsson, 2013).

4.4 Limitations

Study 1

Study 1 only investigated instant neuro-modulatory effects of mirror visual feedback. Thus, the possibility of use-dependent dynamics in functional brain activity by long-term training with the mirror visual feedback devices cannot be excluded.

Furthermore, it is important to mention that behavioral and neuroimaging data were acquired in healthy volunteers that might show different cortical activation patterns and self-reported mirror illusion capacity than, for example, phantom limb pain patients with altered body representations (Deconinck et al., 2014). In a next step, our findings have to be validated in patient groups. The aim of this study, however, was to relate our findings to other studies using the classical mirror box in healthy subjects (Matthys et al., 2009) and using the same or similar mirror illusion items (Diers et al., 2015).

No additional control conditions like pure motor execution or motor execution with motor imagery (of the non-mirrored limb) were performed. Furthermore, potential differences between mirror visual feedback with and without motor imagery were not evaluated. These control conditions were used by others (Bogdanov, Smith, & Frey, 2012; Diers et al., 2010) to rule out that the recruitment of the sensorimotor cortex was simply driven by motor execution or motor imagery alone that have also been shown to induce activation in sensorimotor representation of the non-mirrored limb (Bogdanov et al., 2012). The main objective of Study 1 was, however, to evaluate the efficacy of the mirror glasses in comparison to the mirror box. Thus, the focus was on identifying differences in brain activation between both mirror tasks rather than the additional effect of the mirror beyond pure motor execution or motor imagery, which was already investigated in previous studies (Diers et al., 2010). Moreover, the performance of the proposed control conditions for two different mirror devices is likely to be too demanding for the subjects within a single measurement.

Moreover, it was expected that the brain activation detected in the primary sensorimotor cortex corresponds to the representation of the hand. A separate functional region of interest analysis, however, was not performed to validate the actual position of the hand representation (Bogdanov et al., 2012). A simple hand execution task with unilateral movements of both hands would allow delineating the sensorimotor hand representations.

It is possible that it was more comfortable for the subjects to perform the mirror glasses compared to the mirror box task. The mirror box has spatial limitations according to the degrees of freedom for movements and visualization in the MRI-scanner that might lead to a shift in hand posture and discomfort in the subject (Murray et al., 2007; Walsh and Bannister, 2010).

Study 2

In Study 2 the perception of evoked phantom sensations was confounded by brain activity exclusively associated with the stimulation itself, rendering the identification of brain activity unique to evoked phantom sensations intrinsically difficult. Therefore, brain activation during the elicitation of phantom sensations was contrasted with brain activation during the stimulation of a control body site without phantom sensations using the same stimulus parameters. The control body site was either the anatomically matched contralateral body site or an adjacent site with comparable sensory-discriminative properties.

Evoked phantom sensations were elicited by two stimulation devices: tactile stimulations using a pneumatic stimulator (*N*=9) and electrically, using surface electrodes (*N*=3 amputees). However, we used the same stimulation parameters for both body sites in the within-subjects. Thus, differences in brain activation related to the stimulation-devices are assumed to cancel-out in the contrast we used to determine brain activation related to evoked phantom sensations. Furthermore, we contrasted brain activation during evoked phantom sensations with brain activation during stimulation of matched body site in yoked healthy persons to further validate the specificity of brain activations specific to evoked phantom sensations.

We conducted a block design with fixed block lengths potentially leading to expectancy effects related to the elicitation of evoked phantom sensations. However, we could not avoid expectation effects since we were further interested in the

perceived intensity of evoked phantom sensations assessed following each block. The intensity of evoked phantom sensations was assessed to detect potential habituation effects across blocks and to assess if the evoked phantom sensations vanished after cessation of the stimulus. Alternatively, evoked phantom sensations could also be assessed using an event-related design with continuous ratings on the intensity of phantom sensations. However, we distinguished between the mere presence and absence of evoked phantom sensations and the intensity since the latter might reflect a more general magnitude coding that is not necessarily specific for thee evoked phantom sensations (Baliki et al., 2009; Davis, Kucyi, & Moayedi, 2015b). Former studies did not account for inter-individual differences or the variability in the perceived intensity of evoked phantom sensations across stimulation trials (Björkman et al., 2012; Flor et al., 2000). Noteworthy, the participants were not naïve to the study goal of investigating evoked phantom sensations.

4.5 Outlook

It is of interest to evaluate the therapeutic efficacy of mirror glasses in individual patient groups in a longitudinal study. The potential superiority of the mirror glasses in inducing mirror illusions compared to the mirror box might become evident with extensive practice reducing head movements and thus avoiding biophysically implausible visualizations of the affected limb. Moreover, the type of instruction and the setup during mirror therapy seems to be relevant for the therapeutic outcome. For instance, mirror visual feedback seems to be more efficient when combined with motor imagery (Deconinck et al., 2014).

One finding of Study 1 was the presence of functional coupling between primary sensorimotor hand representations in the mirror glasses condition, which was absent in the mirror box condition. These findings indicate that conceptual differences between mirror visual feedback devices and setups might be associated with different neural mechanisms of multisensory integration. The results of Study 1 emphasize the importance for a systematic investigation of the conceptual factors determining differences in the induction of mirror illusions and associated brain correlates found with different mirror visual feedback devices (Diers et al., 2010; Murray et al., 2007; Walsh and Bannister, 2010). Thus, it is important to standardize mirror illusion setups and to identify the contextual factors for successful mirror therapy of a given mirror visual feedback device (Bogdanov et al., 2012).

As discussed in section 4.3, non-painful phantom phenomena such as the telescoping phenomenon or evoked phantom sensations have been systematically manipulated within body illusion setups to increase acceptance and usability of prostheses or to develop novel approaches in the treatment of phantom pain. In those studies, however, evoked phantom sensations were triggered at the residual limb. It remains to be elucidated if evoked phantom sensations elicited from the residual limb are similar to the phantom sensations elicited from remote body sites, revealing a comparable therapeutic potential.

Neuromodulation techniques such as transcranial magnetic stimulation enable the user to experimentally manipulate certain brain regions being stimulated to establish structure-function relationships. Therefore, the causal role of certain brain areas for a specific task-context such as the perception of evoked phantom sensations can be determined. Study 2 identified targetable cortical sites, like the ventral inferior frontal or the posterior parietal cortices, which can be probed by transcranial magnetic stimulation to gain a mechanistic understanding of the role of these brain regions for the perception of phantom phenomena.

5 SUMMARY

A disturbed body perception is characteristic for various neurological and mental disorders and becomes particularly evident in phantom phenomena after limb amputation. Body illusions, such as mirror visual feedback (MVF) illusions, have been shown to be efficient in treating chronic pain and to be further related to a reversal of cortical reorganization. The present thesis aimed at identifying the neural circuitry of illusory body perception in healthy subjects and unilateral upper-limb amputees using functional magnetic resonance imaging. Study 1 investigated the self-reported mirror illusion capacity and the neural correlates of a novel MVF-device (the mirror glasses) in comparison to the well-established mirror box in healthy persons. Study 2 investigated the neural circuitry of stimulus-evoked non-painful phantom phenomena in unilateral upper-limb amputees.

During mirror illusions, movements of the affected limb are visually recreated by movements of the contralateral limb. The visual recreation of the affected limb seems to be linked to a recruitment of the primary sensorimotor representation of the affected limb. In contrast to the mirror box, the mirror glasses limit the user's view to the visual reflection of the moving hand as opposed to seeing both hands moving in synchrony. It has been proposed that seeing the actually moving limb in addition to the mirror reflection might have a distracting effect. Study 1 evaluated the utility of mirror glasses based on a comparison to the mirror box and tested the hypothesis that increased interhemispheric communication between motor hand representations might drive the activation in the non-mirrored limb representation. The self-reported mirror illusion capacity and brain circuitry were measured in a within-subject design during both MVF-conditions with 20 healthy subjects in counterbalanced order. The self-reported mirror illusion capacity and brain activation patterns did not significantly differ between both mirror tasks. The representation of the non-mirrored hand was recruited in both mirror tasks. A significant increase in interhemispheric connectivity between the hand areas, however, was only found in the mirror glasses condition, suggesting divergent mechanisms for the recruitment of the non-mirrored hand representation between both mirror tasks.

Most amputees still perceive their amputated limb (phantom limb awareness). Phantom phenomena comprise a variety of non-painful and painful sensations

allocated to the amputated limb. Some amputees experience non-painful phantom phenomena when the residual limb or other parts of the body are stimulated (evoked phantom sensations). The neural correlates of non-painful phantom phenomena remain unknown. Study 2 aimed to identify the neural circuitry of evoked non-painful phantom sensations. Twelve upper-limb amputees who reliably perceived non-painful phantom sensations upon stimulation of distal body parts and 12 yoked controls (matched for sex and age) were investigated. Amputees were stimulated at a body site eliciting phantom sensation with a stimulus related on- and offset and a control site without illusory perception. Controls were stimulated at matched body sites. A conjunction analysis showed specificity of the left ventral premotor and inferior frontal cortices (BA44/45) for the perception of referred sensations. Generalized psychophysiological interaction analyses revealed a widespread network showing significant positive intra-parietal and fronto-parietal connectivity. Our study indicates a high convergence between the neural correlates of non-painful phantom sensations and (other) body illusions.

Both studies of the present thesis offer new insights into the understanding the neuronal basis of illusory body perception. Such illusory body perceptions are frequent in chronic pain and targeting these distortions of body perception has been shown to be fruitful for relieving pain and disability.

6 REFERENCES (INTRODUCTION AND GENERAL DISCUSSION)

Andoh, J., Diers, M., Milde, C., Köppe, C., Kleinböhl, D., & Flor, H. (2017). Neural correlates of evoked phantom limb sensations. *Biological Psychology*, 126(10). 89-97, doi:10.1016/j.biopsycho.2017.04.009

Appenzeller, O., & Bicknell, J. M. (1969). Effects of nervous system lesions on phantom experience in amputees. *Neurology*, *19*(2), 141–6. http://dx.doi.org/10.1212/WNL.19.2.141

Apps, M. A. J., Tajadura-Jiménez, A., Sereno, M., Blanke, O., & Tsakiris, M. (2015). Plasticity in unimodal and multimodal brain areas reflects multisensory changes in self-face identification. *Cerebral Cortex (New York, NY: 1991)*, *25*(1), 46–55. doi:10.1093/cercor/bht199

Avanzino, L., Raffo, A., Pelosin, E., Ogliastro, C., Marchese, R., Ruggeri, P., & Abbruzzese, G. (2014). Training based on mirror visual feedback influences transcallosal communication. *European Journal of Neuroscience*, *40*(3), 2581–2588. doi:10.1111/ejn.12615

Avillac, M., Ben Hamed, S., & Duhamel, J.-R. (2007). Multisensory integration in the ventral intraparietal area of the macaque monkey. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *27*(8), 1922–32. doi:10.1523/JNEUROSCI.2646-06.2007

Azañón, E., Longo, M. R., Soto-Faraco, S., & Haggard, P. (2010). The posterior parietal cortex remaps touch into external space. *Current Biology : CB*, *20*(14), 1304–9. doi:10.1016/j.cub.2010.05.063

Azañón, E., & Soto-Faraco, S. (2008). Changing reference frames during the encoding of tactile events. *Current Biology : CB*, *18*(14), 1044–9. doi:10.1016/j.cub.2008.06.045

Baliki, M. N., Geha, P. Y., & Apkarian, A. V. (2009). Parsing pain perception between nociceptive representation and magnitude estimation. *Journal of Neurophysiology*, *101*(2), 875–87. doi:10.1152/jn.91100.2008

Baron, R., & Maier, C. (1995). Phantom limb pain: are cutaneous nociceptors and spinothalamic neurons involved in the signaling and maintenance of

spontaneous and touch-evoked pain? A case report. *Pain*, *60*(2), 223–8.

Bekrater-Bodmann, R., Foell, J., & Flor, H. (2011). Relationship between bodily illusions and pain syndromes. *Pain Management*, *1*(3), 217–228. doi:10.2217/pmt.11.20

Bekrater-Bodmann, R., Schredl, M., Diers, M., Reinhard, I., Foell, J., Trojan, J., … Flor, H. (2015). Post-amputation pain is associated with the recall of an impaired body representation in dreams-results from a nation-wide survey on limb amputees. *PloS One*, *10*(3), e0119552. doi:10.1371/journal.pone.0119552

Berlucchi, G., & Aglioti, S. M. (2010). The body in the brain revisited. *Experimental Brain Research*, *200*(1), 25–35. doi:10.1007/s00221-009-1970-7

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

Björkman, A., Weibull, A., Olsrud, J., Ehrsson, H. H., Rosén, B., & Björkman-Burtscher, I. M. (2012). Phantom digit somatotopy: a functional magnetic resonance imaging study in forearm amputees. *The European Journal of Neuroscience*, *36*(1), 2098–106. doi:10.1111/j.1460-9568.2012.08099.x

Blanke, O. (2012). Multisensory brain mechanisms of bodily self-consciousness. *Nature Reviews Neuroscience*, *13*(8), 556–571. doi:10.1038/nrn3292

Blanke, O., Slater, M., & Serino, A. (2015). Behavioral, Neural, & Computational Principles of Bodily Self-Consciousness. *Neuron*, *88*(1), 145–166. doi:10.1016/j.neuron.2015.09.029

Blankenburg, F., Ruff, C. C., Deichmann, R., Rees, G., & Driver, J. (2006). The cutaneous rabbit illusion affects human primary sensory cortex somatotopically. *PLoS Biology*, *4*(3), e69. doi:10.1371/journal.pbio.0040069

Bogdanov, S., Smith, J., & Frey, S. H. (2012). Former hand territory activity increases after amputation during intact hand movements, but is unaffected by illusory visual feedback. *Neurorehabilitation and Neural Repair*, *26*(6), 604–15.

Bolognini, N., Olgiati, E., Maravita, A., Ferraro, F., & Fregni, F. (2013). Motor and parietal cortex stimulation for phantom limb pain and sensations. *Pain*, *154*(8),

1274–1280. doi:10.1016/j.pain.2013.03.040

Bolognini, N., Spandri, V., Ferraro, F., Salmaggi, A., Molinari, A. C. L., Fregni, F., … Garcia-Larrea, L. (2015). Immediate and Sustained Effects of 5-Day Transcranial Direct Current Stimulation of the Motor Cortex in Phantom Limb Pain. *The Journal of Pain : Official Journal of the American Pain Society*, *16*(7), 657–65. doi:10.1016/j.jpain.2015.03.013

Bonnier, P. (1905). L'Aschématie [Aschematia]. *Revue Neurologique (Paris)*, *13*, 605–609.

Borsook, D., Becerra, L., Fishman, S., Edwards, A., Jennings, C. L., Stojanovic, M., … Breiter, H. (1998). Acute plasticity in the human somatosensory cortex following amputation. *Neuroreport*, *9*(6), 1013–7.

Botvinick, M., & Cohen, J. (1998). Rubber hands "feel" touch that eyes see. *Nature*, *391*(6669), 756–756. doi:10.1038/35784

Buchheit, T., Van de Ven, T., John Hsia, H.-L., McDuffie, M., MacLeod, D. B., White, W., … Shaw, A. D. (2015). Pain Phenotypes and Associated Clinical Risk Factors Following Traumatic Amputation: Results from Veterans Integrated Pain Evaluation Research (VIPER). *Pain Medicine (Malden, Mass.)*. doi:10.1111/pme.12848

Calford, M. B., & Tweedale, R. (1991). C-fibres provide a source of masking inhibition to primary somatosensory cortex. *Proceedings. Biological Sciences / The Royal Society*, *243*(1308), 269–75. doi:10.1098/rspb.1991.0041

Carlen, P. L., Wall, P. D., Nadvorna, H., & Steinbach, T. (1978). Phantom limbs and related phenomena in recent traumatic amputations. *Neurology*, *28*(3), 211–7.

Chan, B. L., Witt, R., Charrow, A. P., Magee, A., Howard, R., Pasquina, P. F., … Tsao, J. W. (2007). Mirror therapy for phantom limb pain. *New England Journal of Medicine*, *357*(21), 2206–2207. doi:10.1056/NEJMc071927

Chen, L. M., Friedman, R. M., & Roe, A. W. (2003). Optical imaging of a tactile illusion in area 3b of the primary somatosensory cortex. *Science (New York, N.Y.)*, *302*(5646), 881–885. doi:10.1126/science.1087846

Christ, O., & Reiner, M. (2014). Perspectives and possible applications of the rubber hand and virtual hand illusion in non-invasive rehabilitation: Technological

improvements and their consequences. *Neuroscience and Biobehavioral Reviews*, *44*, 33–44. doi:10.1016/j.neubiorev.2014.02.013

Churchill, J. D., Arnold, L. L., & Garraghty, P. E. (2001). Somatotopic reorganization in the brainstem and thalamus following peripheral nerve injury in adult primates. *Brain Research*, *910*(1–2), 142–52.

Costantini, M., & Haggard, P. (2007). The rubber hand illusion: sensitivity and reference frame for body ownership. *Consciousness and Cognition*, *16*(2), 229–40. doi:10.1016/j.concog.2007.01.001

Davis, K. D., Kucyi, A., & Moayedi, M. (2015). The pain switch: an "ouch" detector. *Pain*, *156*(11), 2164–2166.

de Preester, H., & Tsakiris, M. (2009). Body-extension versus body-incorporation: Is there a need for a body-model? *Phenomenology and the Cognitive Sciences*, *8*(3), 307–319. doi:10.1007/s11097-009-9121-y

de Vignemont, F. (2010). Body schema and body image-Pros and cons. *Neuropsychologia*, *48*(3), 669–680. doi:10.1016/j.neuropsychologia.2009.09.022

Deconinck, F., Smorenburg, A. R. P., Benham, A., Ledebt, A., Feltham, M. G., & Savelsbergh, G. J. P. (2014). Reflections on Mirror Therapy: A Systematic Review of the Effect of Mirror Visual Feedback on the Brain. *Neurorehabilitation and Neural Repair*, *29*(4), 349–361. doi:10.1177/1545968314546134

Desmond, D. M., & MacLachlan, M. (2010). Prevalence and characteristics of phantom limb pain and residual limb pain in the long term after upper limb amputation. *International Journal of Rehabilitation Research,* *33*(3), 279–82. doi:10.1097/MRR.0b013e328336388d

Devor, M. (2005). Response of injured nerve. In M. Koltzenburg & S. B. McMahon (Eds.), *Textbook of Pain* (4th ed., pp. 905–927). Amsterdam: Elsevier.

Diers, M., Christmann, C., Koeppe, C., Ruf, M., & Flor, H. (2010). Mirrored, imagined and executed movements differentially activate sensorimotor cortex in amputees with and without phantom limb pain. *Pain*, *149*(2), 296–304. Journal Article. doi:10.1016/j.pain.2010.02.020

Diers, M., Kamping, S., Kirsch, P., Rance, M., Bekrater-Bodmann, R., Foell, J., … Flor, H. (2015). Illusion-related brain activations: A new virtual reality mirror box

system for use during functional magnetic resonance imaging. *Brain Res*, *1594*, 173–182. doi:10.1016/j.brainres.2014.11.001.

Dietrich, C., Walter-Walsh, K., Preissler, S., Hofmann, G. O., Witte, O. W., Miltner, W. H. R., & Weiss, T. (2012). Sensory feedback prosthesis reduces phantom limb pain: proof of a principle. *Neuroscience Letters*, *507*(2), 97–100. doi:10.1016/j.neulet.2011.10.068

Ehrsson, H., Holmes, N. P., & Passingham, R. E. (2005). Touching a Rubber Hand: Feeling of Body Ownership Is Associated with Activity in Multisensory Brain Areas. *Journal of Neuroscience*, *25*(45), 10564–10573. doi:10.1523/JNEUROSCI.0800-05.2005

Ehrsson, H., Rosen, B., Stockselius, A., Ragno, C., Kohler, P., & Lundborg, G. (2008). Upper limb amputees can be induced to experience a rubber hand as their own. *Brain*, *131*(12), 3443–3452. doi:10.1093/brain/awn297

Ehrsson, H., Spence, C., & Passingham, R. E. (2004). That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. *Science (New York, N.Y.)*, *305*(5685), 875–7. doi:10.1126/science.1097011

Ephraim, P. L., Wegener, S. T., MacKenzie, E. J., Dillingham, T. R., & Pezzin, L. E. (2005). Phantom pain, residual limb pain, and back pain in amputees: results of a national survey. *Archives of Physical Medicine and Rehabilitation*, *86*(10), 1910–9. doi:10.1016/j.apmr.2005.03.031

Ezendam, D., Bongers, R. M., & Jannink, M. J. (2009). Systematic review of the effectiveness of mirror therapy in upper extremity function. *Disability and Rehabilitation*, *31*(26), 2135–49. doi:10.3109/09638280902887768

Feinberg, T. E., & Venneri, A. (2014). Somatoparaphrenia: Evolving theories and concepts. *Cortex*, *61*, 74–80. doi:10.1016/j.cortex.2014.07.004

Flor, H. (2000). The functional organization of the brain in chronic pain. *Progress in Brain Research*, *129*, 313–22. doi:10.1016/S0079-6123(00)29023-7

Flor, H. (2012). New developments in the understanding and management of persistent pain. *Current Opinion in Psychiatry*, *25*(2), 109–113. doi:10.1097/YCO.0b013e3283503510

Flor, H., Braun, C., Elbert, T., & Birbaumer, N. (1997). Extensive reorganization of

primary somatosensory cortex in chronic back pain patients. *Neuroscience Letters*, *224*(1), 5–8.

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

Flor, H., Elbert, T., Mühlnickel, W., Pantev, C., Wienbruch, C., & Taub, E. (1998). Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. *Experimental Brain Research*, *119*(2), 205–212. doi:10.1007/s002210050334

Flor, H., Mu, C. A. W., Karl, A., Denke, C., Gru, S., Kurth, R., & Taub, E. (2000). A neural substrate for nonpainful phantom limb phenomena. *Neuroreport*, *11*(7), 1407–1411.

Flor, H., Nikolajsen, L., Jensen, T., & Staehelin Jensen, T. (2006). Phantom limb pain: a case of maladaptive CNS plasticity? *Nature Reviews Neuroscience*, *7*(11), 873–881. doi:10.1038/nrn1991

Foell, J., Bekrater-Bodmann, R., Diers, M., & Flor, H. (2014). Mirror therapy for phantom limb pain: Brain changes and the role of body representation. *European Journal of Pain (London, England)*, *18*(5), 1–11. doi:10.1002/j.1532-2149.2013.00433.x

Foell, J., Bekrater-Bodmann, R., Flor, H., & Cole, J. (2011). Phantom limb pain after lower limb trauma: origins and treatments. *The International Journal of Lower Extremity Wounds*, *10*(4), 224–35.   doi:10.1177/1534734611428730

Fotopoulou, A., Jenkinson, P. M., Tsakiris, M., Haggard, P., Rudd, A., & Kopelman, M. D. (2011). Mirror-view reverses somatoparaphrenia: Dissociation between first- and third-person perspectives on body ownership. *Neuropsychologia*, *49*(14), 3946–3955. doi:10.1016/j.neuropsychologia.2011.10.011

Giummarra, M. J., Georgiou-Karistianis, N., Nicholls, M. E. R., Gibson, S. J., Chou, M., & Bradshaw, J. L. (2011). The menacing phantom: what pulls the trigger? *European Journal of Pain (London, England)*, *15*(7), 691.e1-8. doi:10.1016/j.ejpain.2011.01.005

Grivaz, P., Blanke, O., & Serino, A. (2017). Common and distinct brain regions

processing multisensory bodily signals for peripersonal space and body ownership. *NeuroImage*, *147*(iii), 602–618. doi:10.1016/j.neuroimage.2016.12.052

Grüsser, S. M., Mühlnickel, W., Schaefer, M., Villringer, K., Christmann, C., Koeppe, C., & Flor, H. (2004). Remote activation of referred phantom sensation and cortical reorganization in human upper extremity amputees. *Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation Cérébrale*, *154*(1), 97–102. doi:10.1007/s00221-003-1649-4

Grüsser, S. M., Winter, C., Mühlnickel, W., Denke, C., Karl, A., Villringer, K., & Flor, H. (2001). The relationship of perceptual phenomena and cortical reorganization in upper extremity amputees. *Neuroscience*, *102*(2), 263–72.

Guterstam, A., Gentile, G., & Ehrsson, H. H. (2013). The invisible hand illusion: multisensory integration leads to the embodiment of a discrete volume of empty space. *Journal of Cognitive Neuroscience*, *25*(7), 1078–99. doi:10.1162/jocn_a_00393

Hadoush, H., Mano, H., Sunagawa, T., Nakanishi, K., & Ochi, M. (2013). Optimization of mirror therapy to excite ipsilateral primary motor cortex. *NeuroRehabilitation*, *32*(3), 617–24. doi:10.3233/NRE-130884

Hanley, M. A., Ehde, D. M., Jensen, M., Czerniecki, J., Smith, D. G., & Robinson, L. R. (2009). Chronic pain associated with upper-limb loss. *American Journal of Physical Medicine and Rehabilitation / Association of Academic Physiatrists*, *88*(9), 742–51, 779. doi:10.1097/PHM.0b013e3181b306ec

Head, H., & Holmes, H. (1911). Sensory disturbances from cerebral lesions. *Brain*, *34*, 102–254.

Hill, A. (1999). Phantom limb pain: a review of the literature on attributes and potential mechanisms. *Journal of Pain and Symptom Management*, *17*(2), 125–42.

Hong, J. H., Kwon, H. G., & Jang, S. H. (2011). Probabilistic somatotopy of the spinothalamic pathway at the ventroposterolateral nucleus of the thalamus in the human brain. *AJNR. American Journal of Neuroradiology*, *32*(7), 1358–62. doi:10.3174/ajnr.A2497

Hunter, J., Katz, J., & Davis, K. (2003). The effect of tactile and visual sensory inputs on phantom limb awareness. *Brain*, *126*(Pt 3), 579–589. doi:10.1093/brain/awg054

Hunter, J., Katz, J., & Davis, K. (2005). Dissociation of phantom limb phenomena from stump tactile spatial acuity and sensory thresholds. *Brain : A Journal of Neurology*, *128*(Pt 2), 308–20. doi:10.1093/brain/awh350

Hunter, J., Katz, J., & Davis, K. (2008). Stability of phantom limb phenomena after upper limb amputation: a longitudinal study. *Neuroscience*, *156*(4), 939–49. doi:10.1016/j.neuroscience.2008.07.053

Invernizzi, M., Negrini, S., Carda, S., Lanzotti, L., Cisari, C., Baricich, A., … Mt, W. (2012). The value of adding mirror therapy for upper limb motor recovery of subacute stroke patients: a randomized controlled trial, *48*, 1–7.

Jensen, T. S., Krebs, B., Nielsen, J., & Rasmussen, P. (1985). Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation limb pain. *Pain*, *21*(3), 267–78.

Jones, E. G., & Pons, T. P. (1998). Thalamic and brainstem contributions to large-scale plasticity of primate somatosensory cortex. *Science (New York, N.Y.)*, *282*(5391), 1121–5.

Karl, A., Birbaumer, N., Lutzenberger, W., Cohen, L. G., & Flor, H. (2001). Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. *Journal of Neuroscience*, *21*(10), 3609–3618.

Katz, J. (1992). Psychophysiological contributions to phantom limbs. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, *37*(5), 282–98.

Katz, J., & Melzack, R. (1990). Pain "memories" in phantom limbs: review and clinical observations. *Pain*, *43*(3), 319–36.

Kilteni, K., Normand, J.-M., Sanchez-Vives, M. V, & Slater, M. (2012). Extending body space in immersive virtual reality: a very long arm illusion. *PloS One*, *7*(7), e40867. doi:10.1371/journal.pone.0040867

Knecht, S., Henningsen, H., Elbert, T., Flor, H., Höhling, C., Pantev, C., & Taub, E. (1996). Reorganizational and perceptional changes after amputation. *Brain : A Journal of Neurology*, *119 (Pt 4)*, 1213–9.

Knecht, S., Henningsen, H., Höhling, C., Elbert, T., Flor, H., Pantev, C., & Taub, E. (1998). Plasticity of plasticity? Changes in the pattern of perceptual correlates of reorganization after amputation. *Brain : A Journal of Neurology, 121 (Pt 4)*, 717–24.

Knecht, S., Kunesch, E., & Schnitzler, A. (1996). Parallel and serial processing of haptic information in man: effects of parietal lesions on sensorimotor hand function. *Neuropsychologia*, *34*(7), 669–87.

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

Läppchen, C. H., Ringer, T., Blessin, J., Seidel, G., Grieshammer, S., Lange, R., & Hamzei, F. (2012). Optical illusion alters M1 excitability after mirror therapy: a TMS study. *Journal of Neurophysiology*, *108*(10), 2857–61. doi:10.1152/jn.00321.2012

Lenggenhager, B., Tadi, T., Metzinger, T., & Blanke, O. (2007). Video ergo sum: manipulating bodily self-consciousness. *Science (New York, N.Y.)*, *317*(5841), 1096–9. doi:10.1126/science.1143439

Lewis, J. S., Kersten, P., McPherson, K. M., Taylor, G. J., Harris, N., McCabe, C. S., & Blake, D. R. (2010). Wherever is my arm? Impaired upper limb position accuracy in Complex Regional Pain Syndrome. *Pain*, *149*(3), 463–469.

Lloyd, D. M. (2007). Spatial limits on referred touch to an alien limb may reflect boundaries of visuo-tactile peripersonal space surrounding the hand. *Brain and Cognition*, *64*(1), 104–9. doi:10.1016/j.bandc.2006.09.013

Longo, M. R., Betti, V., Aglioti, S. M., & Haggard, P. (2009). Visually induced analgesia: seeing the body reduces pain. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *29*(39), 12125–12130.

Lotze, M., Flor, H., Grodd, W., Larbig, W., & Birbaumer, N. (2001). Phantom movements and pain. An fMRI study in upper limb amputees. *Brain*, *124*(Pt 11), 2268–77. doi:10.1093/brain/124.11.2268

Lotze, M., Grodd, W., Birbaumer, N., Erb, M., Huse, E., & Flor, H. (1999). Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb

pain? *Nature Neuroscience, 2*(6), 501–2. doi:10.1038/9145

MacIver, K., Lloyd, D. M., Kelly, S., Roberts, N., & Nurmikko, T. (2008). Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. *Brain : A Journal of Neurology, 131*(Pt 8), 2181–91.   doi:10.1093/brain/awn124

Maihöfner, C., Neundörfer, B., Birklein, F., & Handwerker, H. O. (2006). Mislocalization of tactile stimulation in patients with complex regional pain syndrome. *Journal of Neurology, 253*(6), 772–9. doi:10.1007/s00415-006-0117-z

Maravita, A., & Iriki, A. (2004). Tools for the body (schema). *Trends in Cognitive Sciences, 8*(2), 79–86. doi:10.1016/j.tics.2003.12.008

Mars, R. B., Jbabdi, S., Sallet, J., O'Reilly, J. X., Croxson, P. L., Olivier, E., … Rushworth, M. F. S. (2011). Diffusion-Weighted Imaging Tractography-Based Parcellation of the Human Parietal Cortex and Comparison with Human and Macaque Resting-State Functional Connectivity. *Journal of Neuroscience, 31*(11), 4087–4100. doi:10.1523/JNEUROSCI.5102-10.2011

Marx, J. J., Iannetti, G. D., Thömke, F., Fitzek, S., Urban, P. P., Stoeter, P., … Hopf, H. C. (2005). Somatotopic organization of the corticospinal tract in the human brainstem: a MRI-based mapping analysis. *Annals of Neurology, 57*(6), 824–31. doi:10.1002/ana.20487

Matthys, K., Smits, M., Van der Geest, J. N., Van der Lugt, A., Seurinck, R., Stam, H. J., & Selles, R. W. (2009). Mirror-induced visual illusion of hand movements: a functional magnetic resonance imaging study. *Archives of Physical Medicine and Rehabilitation, 90*(4), 675–81. doi:10.1016/j.apmr.2008.09.571

McCabe, C., Haigh, R. C., & Blake, D. R. (2008). Mirror visual feedback for the treatment of complex regional pain syndrome (type 1). *Current Pain and Headache Reports, 12*(2), 103–107. doi:10.1007/s11916-008-0020-7

McCabe, C., Haigh, R. C., Ring, E. F., Halligan, P. W., Wall, P. D., & Blake, D. R. (2003). A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). *Rheumatology (Oxford), 42*(1), 97–101. doi:10.1093/rheumatology/keg041

Medina, J., & Coslett, H. B. (2010). From maps to form to space: touch and the body schema. *Neuropsychologia, 48*(3), 645–54.

doi:10.1016/j.neuropsychologia.2009.08.017

Merzenich, M. M., Nelson, R. J., Stryker, M. P., Cynader, M. S., Schoppmann, A., & Zook, J. M. (1984). Somatosensory cortical map changes following digit amputation in adult monkeys. *Journal of Comparative Neurology*, *224*(4), 591–605.

Millonig, A., Bodner, T., Donnemiller, E., Wolf, E., & Unterberger, I. (2011). Supernumerary phantom limb as a rare symptom of epileptic seizures - case report and literature review. *Epilepsia*, *52*(8), e97–e100. doi:10.1111/j.1528-1167.2011.03156.x

Moore, C. I., Stern, C. E., Dunbar, C., Kostyk, S. K., Gehi, A., & Corkin, S. (2000). Referred phantom sensations and cortical reorganization after spinal cord injury in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(26), 14703–8. doi:10.1073/pnas.250348997

Moseley, G. (2006). Graded motor imagery for pathologic pain: a randomized controlled trial. *Neurology*, *67*(12), 2129–34. doi:10.1212/01.wnl.0000249112.56935.32

Moseley, G., & Flor, H. (2012). Targeting Cortical Representations in the Treatment of Chronic Pain: A Review. *Neurorehabilitation and Neural Repair*, *26*(6), 646–652. doi:10.1177/1545968311433209

Moseley, G., Gallace, A., & Spence, C. (2012). Bodily illusions in health and disease: Physiological and clinical perspectives and the concept of a cortical "body matrix." *Neuroscience and Biobehavioral Reviews*.

Murray, C. D., Pettifer, S., Howard, T., Patchick, E. L., Caillette, F., Kulkarni, J., & Bamford, C. (2007). The treatment of phantom limb pain using immersive virtual reality: three case studies. *Disability and Rehabilitation*, *29*(18), 1465–1469. doi:10.1080/09638280601107385

Nojima, I., Mima, T., Koganemaru, S., Thabit, M. N., Fukuyama, H., & Kawamata, T. (2012). Human Motor Plasticity Induced by Mirror Visual Feedback. *Journal of Neuroscience*, *32*(4), 1293–1300. doi:10.1523/JNEUROSCI.5364-11.2012

Nojima, I., Oga, T., Fukuyama, H., Kawamata, T., & Mima, T. (2013). Mirror visual feedback can induce motor learning in patients with callosal disconnection.

Experimental Brain Research, 1–5. doi:10.1007/s00221-013-3486-4

Nyström, B., & Hagbarth, K. E. (1981). Microelectrode recordings from transected nerves in amputees with phantom limb pain. *Neuroscience Letters*, *27*(2), 211–6.

Paillard, J. (1980). Le corps situé et le corps identifié. Une approche psychophysiologique de la notion de schéma corporel. *Revue Medicale de La Suisse Romande*, *100*, 129–141.

Paillard, J. (1999). Body Schema and Body Image - A Double Dissociation in Deafferented Patients. In G. N. Gantchev, S. Mori, & J. Massion (Eds.), *Motor control, today and tomorrow* (Vol. 48, pp. 197–214). Prof. M. Drinov Academic Publishing House.

Palermo, L., Di Vita, A., Piccardi, L., Traballesi, M., & Guariglia, C. (2014). Bottom-up and top-down processes in body representation: a study of brain-damaged and amputee patients. *Neuropsychology*, *28*(5), 772–781. doi:10.1037/neu0000086

Penfield, W. and, & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, *6*(4), 389–443.

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

Purves, D., Augustine, G. J., Fitzpatrick, D., Hall, W. C., LaMantia, A.-S., McNamara, J. O., & White, L. E. (2008a). The somatic sensory system. In D. Fitzpatrick (Ed.), *Neuroscience* (4th ed., pp. 206–229). Sunderland: Sinauer Associates.

Purves, D., Augustine, G. J., Fitzpatrick, D., Hall, W. C., LaMantia, A.-S., McNamara, J. O., & White, L. E. (2008b). Upper motor neuron control of the brainstem and spinal cord. In W. C. Hall & L. White (Eds.), *Neuroscience* (4th ed., pp. 423–452). Sunderland: Sinauer Associates.

Raffin, E., Richard, N., Giraux, P., & Reilly, K. T. (2016). Primary motor cortex changes after amputation correlate with phantom limb pain and the ability to move the phantom limb. *NeuroImage*, *130*, 134–144. doi:10.1016/j.neuroimage.2016.01.063

Raichle, K. A., Osborne, T. L., Jensen, M. P., Ehde, D. M., Smith, D. G., & Robinson,

L. R. (2015). Preoperative state anxiety, acute postoperative pain, and analgesic use in persons undergoing lower limb amputation. *The Clinical Journal of Pain*, *31*(8), 699–706. doi:10.1097/AJP.0000000000000150

Ramachandran, V., & Rogers-Ramachandran, D. (1996). Synaesthesia in phantom limbs induced with mirrors. *Proceedings. Biological Sciences / The Royal Society*, *263*(1369), 377–86. doi:10.1098/rspb.1996.0058

Ramachandran, V., Stewart, M., & Rogers-Ramachandran, D. (1992). Perceptual Correlates of Massive Cortical Reorganization. *Neuroreport*, *3*(7), 583–586. doi:10.1097/00001756-199207000-00009

Rizzolatti, G., Scandolara, C., Matelli, M., & Gentilucci, M. (1981a). Afferent properties of periarcuate neurons in macaque monkeys. I. Somatosensory responses. *Behavioural Brain Research*, *2*(2), 125–146. doi:10.1016/0166-4328(81)90052-8

Rizzolatti, G., Scandolara, C., Matelli, M., & Gentilucci, M. (1981b). Afferent properties of periarcuate neurons in macaque monkeys. II. Visual responses. *Behavioural Brain Research*, *2*(2), 147–163. doi:10.1016/0166-4328(81)90053-X

Rosén, B., Ehrsson, H. H., Antfolk, C., Cipriani, C., Sebelius, F., & Lundborg, G. (2009). Referral of sensation to an advanced humanoid robotic hand prosthesis. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery / Nordisk Plastikkirurgisk Forening [and] Nordisk Klubb for Handkirurgi*, *43*(5), 260–6. doi:10.3109/02844310903113107

Rousseaux, M., Honoré, J., & Saj, A. (2014). Body representations and brain damage. *Neurophysiologie Clinique*, *44*(1), 59–67. doi:10.1016/j.neucli.2013.10.130

Ruzzoli, M., & Soto-Faraco, S. (2014). Alpha Stimulation of the Human Parietal Cortex Attunes Tactile Perception to External Space. *Current Biology*, *24*(3), 329–332. doi:10.1016/j.cub.2013.12.029

Schley, M., Wilms, P., Toepfner, S., Schaller, H.-P., Schmelz, M., Konrad, C. J., & Birbaumer, N. (2008). Painful and nonpainful phantom and stump sensations in acute traumatic amputees. *The Journal of Trauma*, *65*(4), 858–864. doi:10.1097/TA.0b013e31812eed9e

Schmalzl, L., Kalckert, A., Ragnö, C., & Ehrsson, H. H. (2013). Neural correlates of the rubber hand illusion in amputees: A report of two cases. *Neurocase, 20*(4), 407–420. doi:10.1080/13554794.2013.791861

Schmalzl, L., Ragnö, C., & Ehrsson, H. H. (2013). An alternative to traditional mirror therapy: illusory touch can reduce phantom pain when illusory movement does not. *The Clinical Journal of Pain, 29*(10), e10-8. doi:10.1097/AJP.0b013e3182850573

Schwoebel, J., & Coslett, H. B. (2005). Evidence for multiple, distinct representations of the human body. *Journal of Cognitive Neuroscience, 17*(4), 543–553.

Senkowski, D., & Heinz, A. (2016). Chronic pain and distorted body image: Implications for multisensory feedback interventions. *Neuroscience and Biobehavioral Reviews, 69*, 252–259. doi:10.1016/j.neubiorev.2016.08.009

Sherman, R. (1995). *Phantom Pain*. New York: Plenum Press.

Sherman, R., Arena, J., Sherman, C., & Ernst, J. (1989). The mystery of phantom limb pain: growing evidence for psychophysiological mechanisms. *Biofeedback Self Regulation, 14*, 267–280.

Sherman, R., Sherman, C., & Parker, L. (1984). Chronic phantom and stump pain among American veterans: results of a survey. *Pain, 18*(1), 83–95.

Soin, A., Fang, Z.-P., & Velasco, J. (2015). Peripheral Neuromodulation to Treat Postamputation Pain. *Progress in Neurological Surgery, 29*, 158–67. doi:10.1159/000434669

Srivastava, A., Taly, A. B., Gupta, A., Murali, T., Noone, M. L., Thirthahalli, J., … Jayakumar, P. N. (2008). Stroke with supernumerary phantom limb: case study, review of literature and pathogenesis. *Acta Neuropsychiatrica, 20*(5), 256–64. doi:10.1111/j.1601-5215.2008.00294.x

Stein, B. E., & Stanford, T. R. (2008). Multisensory integration: current issues from the perspective of the single neuron. *Nature Reviews. Neuroscience, 9*(4), 255–66. doi:10.1038/nrn2331

Stein, B. E., Stanford, T. R., & Rowland, B. A. (2014). Development of multisensory integration from the perspective of the individual neuron. *Nature Reviews. Neuroscience, 15*(8), 520–35.

Taghipour, H., Moharamzad, Y., Mafi, A. R., Amini, A., Naghizadeh, M. M., Soroush, M. R., & Namavari, A. (2009). Quality of life among veterans with war-related unilateral lower extremity amputation: a long-term survey in a prosthesis center in Iran. *Journal of Orthopaedic Trauma*, *23*(7), 525–30. doi:10.1097/BOT.0b013e3181a10241

Takanashi, M., Abe, K., Yanagihara, T., Sakoda, S., Tanaka, H., Hirabuki, N., … Fujita, N. (2003). A functional MRI study of somatotopic representation of somatosensory stimulation in the cerebellum. *Neuroradiology*, *45*(3), 149–52. doi:10.1007/s00234-002-0935-3

Tamura, Y., Shibukawa, Y., Shintani, M., Kaneko, Y., & Ichinohe, T. (2008). Oral structure representation in human somatosensory cortex. *NeuroImage*, *43*(1), 128–135. doi:10.1016/j.neuroimage.2008.06.040

Taoka, M., Toda, T., Hihara, S., Tanaka, M., Iriki, A., & Iwamura, Y. (2016). A systematic analysis of neurons with large somatosensory receptive fields covering multiple body regions in the secondary somatosensory area of macaque monkeys. *Journal of Neurophysiology*, *116*(5), 2152–2162. doi:10.1152/jn.00241.2016

Tomassini, V., Jbabdi, S., Klein, J. C., Behrens, T. E. J., Pozzilli, C., Matthews, P. M., … Johansen-Berg, H. (2007). Diffusion-Weighted Imaging Tractography-Based Parcellation of the Human Lateral Premotor Cortex Identifies Dorsal and Ventral Subregions with Anatomical and Functional Specializations. *Journal of Neuroscience*, *27*(38), 10259–10269. doi:10.1523/JNEUROSCI.2144-07.2007

Tsakiris, M. (2010). My body in the brain: a neurocognitive model of body-ownership. *Neuropsychologia*, *48*(3), 703–12. doi:10.1016/j.neuropsychologia.2009.09.034

Tsakiris, M., Carpenter, L., James, D., & Fotopoulou, A. (2010). Hands only illusion: multisensory integration elicits sense of ownership for body parts but not for non-corporeal objects. *Experimental Brain Research*, *204*(3), 343–352. doi:10.1007/s00221-009-2039-3

Tsakiris, M., Schuetz-Bosbach, S., & Gallagher, S. (2007). On agency and body-ownership: Phenomenological and neurocognitive reflections. *Consciousness and Cognition*, *16*(3), 645–660. doi:10.1016/j.concog.2007.05.012

Tsay, A., Allen, T. J., Proske, U., & Giummarra, M. (2015). Sensing the body in chronic pain: A review of psychophysical studies implicating altered body representation. *Neuroscience & Biobehavioral Reviews*, *52*, 221–232. doi:10.1016/j.neubiorev.2015.03.004

Uddin, L., Kaplan, J. T., Molnar-Szakacs, I., Zaidel, E., & Iacoboni, M. (2005). Self-face recognition activates a frontoparietal network in the right hemisphere: an event-related fMRI study. *NeuroImage*, *25*(3), 926–35. doi:10.1016/j.neuroimage.2004.12.018

Uddin, L., Supekar, K., Amin, H., Rykhlevskaia, E., Nguyen, D. A., Greicius, M. D., & Menon, V. (2010). Dissociable Connectivity within Human Angular Gyrus and Intraparietal Sulcus: Evidence from Functional and Structural Connectivity. *Cerebral Cortex*, *20*(11), 2636–2646. doi:10.1093/cercor/bhq011

Vartiainen, N., Kirveskari, E., Kallio-Laine, K., Kalso, E., & Forss, N. (2009). Cortical reorganization in primary somatosensory cortex in patients with unilateral chronic pain. *The Journal of Pain : Official Journal of the American Pain Society*, *10*(8), 854–9. doi:10.1016/j.jpain.2009.02.006

Vartiainen, N. V, Kirveskari, E., & Forss, N. (2008). Central processing of tactile and nociceptive stimuli in complex regional pain syndrome. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *119*(10), 2380–8. doi:10.1016/j.clinph.2008.06.008

Vase, L., Nikolajsen, L., Christensen, B., Egsgaard, L. L., Arendt-Nielsen, L., Svensson, P., & Staehelin Jensen, T. (2011). Cognitive-emotional sensitization contributes to wind-up-like pain in phantom limb pain patients. *Pain*, *152*(1), 157–62. doi:10.1016/j.pain.2010.10.013

Walsh, G., & Bannister, J. (2010). A device for the relief of phantom limb pain and rehabilitation in stroke. *Optometry and Vision Science : Official Publication of the American Academy of Optometry*, *87*(12), E971-8. doi:10.1097/OPX.0b013e3181fcabc3

Wand, B. M., Keeves, J., Bourgoin, C., George, P. J., Smith, A. J., O'Connell, N. E., & Moseley, G. L. (2013). Mislocalization of sensory information in people with chronic low back pain: a preliminary investigation. *The Clinical Journal of Pain*,

29(8), 737–43. doi:10.1097/AJP.0b013e318274b320

Weeks, S. R., Anderson-Barnes, V. C., & Tsao, J. W. (2010). Phantom Limb Pain. *The Neurologist*, *16*(5), 277–286. doi:10.1097/NRL.0b013e3181edf128

Weiss, T., Miltner, W. H., Adler, T., Brückner, L., & Taub, E. (1999). Decrease in phantom limb pain associated with prosthesis-induced increased use of an amputation stump in humans. *Neuroscience Letters*, *272*(2), 131–4.

Willoch, F., Rosen, G., Tölle, T. R., Oye, I., Wester, H. J., Berner, N., … Bartenstein, P. (2000). Phantom limb pain in the human brain: unraveling neural circuitries of phantom limb sensations using positron emission tomography. *Annals of Neurology*, *48*(6), 842–9.

Yamada, K., Nagakane, Y., Yoshikawa, K., Kizu, O., Ito, H., Kubota, T., … Nishimura, T. (2007). Somatotopic organization of thalamocortical projection fibers as assessed with MR tractography. *Radiology*, *242*(3), 840–5. doi:10.1148/radiol.2423060297

7 CURRICULUM VITAE

Personalien

Name und Vorname: Milde, Christopher

Adresse: H3, 11

                                                       68159 Mannheim

Telefon: 0176-23873323

Geburtsdatum: 12.01.1986

Geburtsort: Emden (Niedersachsen)

Staatsangehörigkeit: deutsch

Familienstand: ledig, keine Kinder

Beschäftigung

2013 – heute   Zentralinstitut für Seelische Gesundheit, Mannheim

                              Institut für Neuropsychologie und Klinische Psychologie

                              Wissenschaftlicher Mitarbeiter

Studium

2009 – 2012   Carl von Ossietzky Universität, Oldenburg

                              Masterstudium der Biologie (Note: 1.1)

14.03.2012   Masterarbeit (Titel: Remember me: Is the retrieval performance for
                              emotional faces especially prone to psychosocial stress?)

2006 – 2009   Carl von Ossietzky Universität, Oldenburg

                              Bachelorstudium der Biologie

07.12.2009   Bachelorarbeit (Titel: Sex Ratio of *Phyllognathopus viguieri*
                              (Maupas, 1892) – A potential example of rare and evolutionary
                              unstable polygenic sex determination)

Schulischer Werdegang

1998-2002	Realschule, Pewsum
2002-2005	Fachgymnasium Gesundheit und Soziales, BBS II, Emden
17.06.2005	Allgemeine Hochschulreife

Mannheim, den 19.09.2017

8 LIST OF PUBLICATIONS

Andoh, J., Milde, C., Frobel, C., Kleinböhl, D., & Flor, H. (2017). Neural correlates of evoked phantom limb sensations. *Biological Psychology*. 126(10): 89-97. doi: 10.1016 /j.biopsycho.2017.04.009.

Diers, M., & Milde, C. (2017). Neuroimaging of chronic pain. In Saba, L. (Ed.) *Neuroimaging of Pain* (pp. 171-214). New York, USA. Springer Business & Science Media.

Li, S., Weerda, R., Milde, C., Wolf, O. T., & Thiel, C. M. (2015). ADRA2B genotype differentially modulates stress-induced neural activity in the amygdala and hippocampus during emotional memory retrieval. *Psychopharmacology*. 232(4): 755-64. doi: 10.1007/s00213-014-3710-3.

Li, S., Weerda, R., Milde, C., Wolf, O. T., & Thiel, C. M. (2014). Effects of acute psychosocial stress on neural activity to emotional and neutral faces in a face recognition memory paradigm. *Brain Imaging and Behavior*. 8(4): 98-610. doi: 10.1007/s11682-013-9287-3.

Milde, C., & Schneider, P. (2017). Das Potenzial empirischer Befunde zur aberranten Körperwahrnehmungen und -kognitionen für die philosophische Theorienbildung. In Schlette, M., Fuchs, T., & Kirchner A. M. (Eds.). *Anthropologie der Wahrnehmung* (Vol. 16, pp. 423-452). Heidelberg, Germany. Universitätsverlag Winter.

Milde, C., Rance, M., Kirsch, P., Trojan, J., Fuchs, X., Foell, J., Bekrater-Bodmann R., Flor, H., & Diers, M. (2015). *Do mirror glasses have the same effect on brain activity as a mirror box? Evidence from a functional magnetic resonance imaging study with healthy subjects.* PLoS One. 27;10(5):e0127694. doi: 10.1371/journal.pone.0127694. eCollection 2015.

9 DANKSAGUNG

Mein Dank gebührt an erster Stelle meiner Doktormutter Prof. Dr. Dr. h.c. Herta Flor, welche mir diese Promotion ermöglichte. Ungeachtet ihres hohen Arbeitspensums, fand sie stets die Zeit mich im wissenschaftlichen Diskurs auf kritische Aspekte meiner Doktorarbeitsstudien aufmerksam zu machen und so meine Dissertation entscheidend zu optimieren.

Besondere Erwähnung soll auch das gesamte PHANTOMMIND-Projektteam finden. Daher gilt mein Dank: PD Dr. Susanne Becker, Dr. Jamila Andoh, Jun.-Prof. Dr. Jörg Trojan, Dr. Bekrater-Bodmann, Dr. Xaver Fuchs, Kristina Staudt sowie Astrid Wolf und Silvia Gubay. Für seine großartige Unterstützung und seine unbegrenzten Geduld in fachlichen Diskursen, möchte ich mich im Speziellen bei dem PHANTOMMIND-Projektkoordinator Prof. Dr. Martin Diers bedanken.

Außerdem bedanke ich mich auf das innigste bei meiner Familie, die mir trotz der großen geografischen Distanz stets eine wertvolle Stütze ist und war.

Überdies möchte ich all meinen Probanden danken.

Durch meine Arbeit am ZI konnte ich auch wertvolle Freundschaften schließen, die mir stets eine große Motivationsstütze sind, und mit denen ich das eine oder andere heitere als auch ernste Gespräch führen durfte.

Für das Gegenlesen meiner Dissertationsschrift danke ich überdies Pia Schneider und Prof. Dr. Martin Diers.

An letzter und zugleich erster Stelle danke ich Martina, die mir immer wieder auf das Neue verdeutlicht, was wirklich wichtig ist.