The Body
and Beyond the Body

Body and space interactions in healthy individuals and patients with acquired brain damage

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Het lichaam en voorbij het lichaam
Lichaam en ruimte interacties in gezonde proefpersonen en patiënten met aangeboren hersenletsel
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

vrijdag 3 november 2023 des middags te 4.15 uur

door

Miranda Smit

geboren op 13 februari 1983
te Avereest

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The research described in this thesis was financially supported by a grant from the Netherlands Organization for Scientific Research (NWO Vici grant 453-10-003) and a Brain Foundation (Hersenstichting) grant to H. Chris Dijkerman.

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Chapter 1

General introduction

Miranda Smit

GENERAL INTRODUCTION

Over the past few years, I have seen many different participants for my studies. All these participants have helped me gain insight in several different concepts regarding body representation and the space surrounding the body, and simultaneously have raised so many additional questions. Next to 'neurotypical' participants I have encountered patients who suffered structurally from body representational problems. One woman thought her arm was not hers, and thought her arm belonged to her partner or believed his arm belonged to her when it was in close proximity. This was particularly scary when she sat in the car, on the passenger seat, and mistook her husband's hand, that was on the gearshift, as her own. At times she became verbally and physically hostile towards her own hand and would hurt her hand. Another patient knew that his body was his, but his body did not feel as such. While he was driving, he viewed his hand as a strange, alien, object. It did not feel like *his* hands were performing these actions, despite having full motor control over them. Hearing all these stories and simultaneously reading about it, I learned to appreciate how these seemingly simple acts, such as reaching for a morning coffee, depend on so many processes which we often take for granted. For instance, I have to 'know' the location of my hand, the location of the cup of coffee, the length and width metrics of my hand, and also how far the cup is in space. Moreover, there might be a chance I have to retract my hand because the cup is still too hot to touch. We are usually not aware of performing these actions, let alone, aware of the given premise that the body that is performing these actions, is actually ours. We usually become aware and learn to appreciate bodily functions when certain acts become difficult to perform e.g., when we do not know how far to reach, when we do not get tactile feedback when the cup is still too hot to touch and leave burn marks, or when the hand feels alien when we reach for that cup. Or even more challenging, we might get burnt when the hot cup of coffee is on the side of our surroundings that is consistently not 'attended' to. These examples might seem odd, but are not unfamiliar after stroke, when hemispatial neglect occurs, especially after right hemispheric damage. In this thesis I will tap into processes concerning the representation of the body and bodily space in both healthy individuals and individuals after stroke. First, I will outline how higher order representations are constructed based on primary sensory input, and which impairments can occur in the process.

The somatosensory system: making sense of the senses

The ability to sense touch involves a complex network called the somatosensory system (Franzen, Johansson & Terenius, 1996). We have specialized receptors for the sensations we feel. If I go back to the previous example where I would like to reach for a cup of coffee, then the proprioceptors of my body will provide information about the muscle length and muscle tension in order for my body to sense the position of my hand relative to the cup (and other body parts and objects). When I actually manage to reach and grasp it, different mechanoreceptors will respond to the texture of the cup and these receptors will also convey information about whether I use pressure while holding it. Moreover, thermoreceptors will tell me whether the coffee is either hot or cold. If the coffee is too hot (beyond 45 degrees Celsius), pain receptors or nociceptors become dominant to signal a warning in order to avoid any damage to my skin.

When touching the cup or grasping for the cup, information travels from these different receptors in my skin, muscles and joints to my brain via different pathways (Figure 1): the spinothalamic pathway and the medial lemniscal pathway. The former pathway processes nociceptive, thermoceptive, and affective tactile information, while the latter pathway processes elementary touch information from mechanoreceptors (i.e., pressure, texture, vibration) and proprioceptive information. In my thesis I will mainly focus on information that travels through this medial lemniscal tract, projects onto the contralateral thalamus and then to the primary somatosensory cortex.

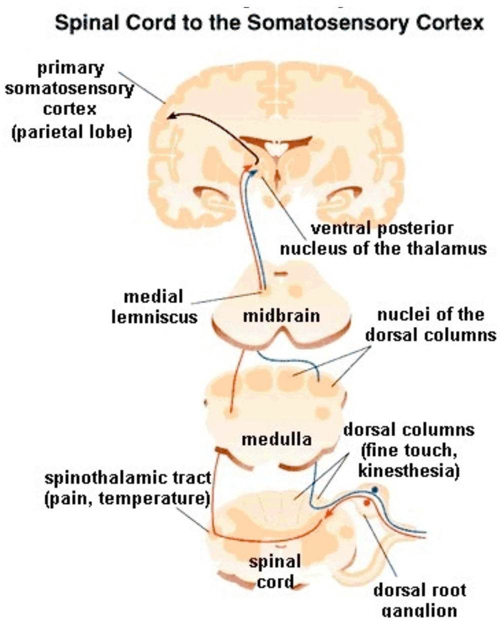

Figure 1. The medial lemniscal and spinothalamic pathways.
From http://www.scholarpedia.org/article/Central_touch_disorders.

In each hemisphere, the primary sensory cortex (S1) consists of a somatotopic blueprint (Figure 2) of the contralateral side of the body; a tactile representation that reflects the relative receptor density of a particular body part, that is, body parts with a higher receptor density employ a larger region in S1 (Penfield, 1950). Thus, the size devoted to a body part is not proportional to its actual size, but to its relative receptor density. Therefore, the hands, and the lips, which have a high receptor density, occupy large regions in S1 (Figure 2).

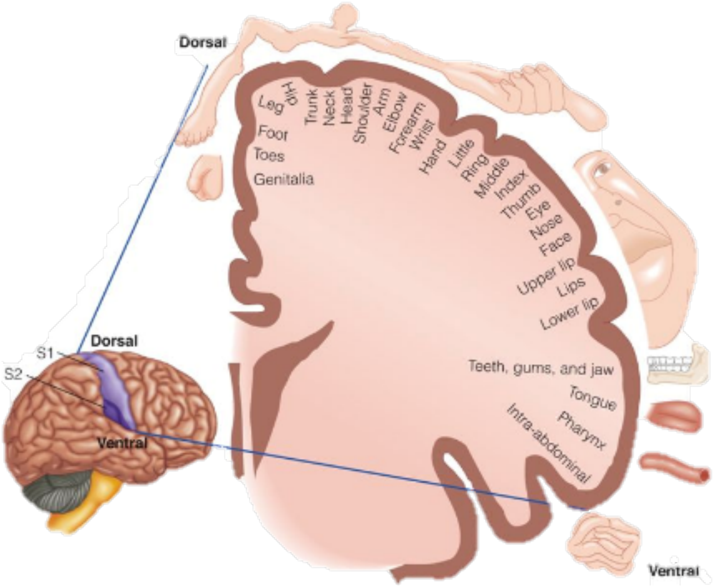

Figure 2. Primary somatosensory cortex. Adapted from Penfield and Rasmussen, 1950. The cerebral cortex of man.

Damage to the primary sensory cortex might result in loss of perception of vibration, proprioception and tactile acuity (fine touch). Patients can be selectively impaired on elementary touch processes (Corkin, 1978) (e.g., without deficits in proprioception or other somatosensory sub modalities), which suggest these characteristics can travel in parallel. The secondary somatosensory cortex (SII) is the region adjacent to somatosensory cortex, located in the parietal operculum. Both SI and SII are reciprocally connected to the thalamus (Catani et al., 2012) and the insula (Augustine, 1996). Similarly, SII also has somatotopic maps of the body. This blueprint is, however, less precise as in SI because of the large bilateral receptive fields (Disbrow, Roberts, Krubitzer, 2000). As a consequence, unilateral stimulation of extremities results in bilateral activation of SII. SII, and its connections to the insula and posterior parietal cortex, is more involved in higher order somatosensory processes, such as tactile attention (Burton, Abend, MacLeod, Sinclair, Snyder, Raichle, 2012) and body perception related processes (Dijkerman & de Haan, 2007).

Perception of body part size and shape

It is a complex process how we process basic somatosensory sensations to achieve higher order body percepts and representations, such as the perceived shape of the body or a body part. In the next section I will discuss how we perceive the body shape (hand shape in particular), structure and dimensions and how we achieve efficient and successful interactions with the outside world (haptic exploration in peripersonal space). Interestingly, there is considerable evidence that distortions present at the level of S1 also influence perception of body size and shape.

Numerous studies in healthy individuals have shown that we perceive our body as highly distorted (Linkenauger**,** Kirby**,** McCulloch & Longo, 2017). Our hand, for instance, is perceived as having shortened fingers and broadened hands (Longo & Haggard 2010, Longo et al., 2012; Longo et al., 2015; Saulton et al., 2014; Saulton et al., 2016, Coelho et al., 2016). The pattern of distortion indeed matches the geometry and tactile acuity of the receptive field on the dorsal side of the hand. These receptive fields are oval-shaped (Powell and Mountcastle, 1959; Brown et al., 1975), hence, there are more receptive field boundaries mediolaterally than proximodistally, and therefore we perceive the overall shape of the hand to be wider than it is long. Weber (1834) observed that the same distance between two touches felt larger on parts of the skin that has smaller receptive fields, hence skin surface with higher tactile acuity. So, tactile perception reflects the distorted characteristics in S1. However, this is not the whole story, since the perceptual distortions do not fully match the cortical magnification in S1 as is shown with the Weber’s illusion. This indicates that the brain somehow attempts to preserve tactile size constancy by rescaling the primary, distorted body-surface representation (Taylor-Clarke, Kennet & Haggard, 2002). Longo et al., (2010) propose a model that this tactile constancy is a product of referencing to a higher form of representation, such as a stored body model. According to Longo, this body model ‘knows’ the metric properties of the body. Evidence for the fact that the perception of our body comes from both primary sensory information and higher order information stems from studies where various illusions mediate tactile distance perception in a top-down manner (Taylor-Clarke et al., 2002; de Vignemont et al., 2005; Tajadura-Jiménez et al., 2012; Longo et al., 2013). In all these studies, somatosensory processing (and distance perception) was influenced by visual experience. The same logic applies for our position sense, which is the ability to know the spatial location of our limbs. Afferent signals (joint receptors and muscle spindles) are involved in providing proprioceptive information. However, immediate afferent signals alone cannot provide information about our arm length or width, it must be referenced to stored body representation ‘knowing’ the metric properties of our body. According to Longo and Haggard (2010) this body model preserves distortions from S1 in an attenuated manner. These distortions are not apparent in the conscious body image, and Longo treats these two representations as distinct (Longo and Haggard, 2012) but on opposite ends on the same continuum (Longo & Haggard, 2017). However, Linkenauger et al. (2015) presented an alternative view on this. On one end of the continuum there is the existence of a more veridical, explicit visually based body representation and on the other end a representation based on somatosensation which is highly distorted. In Longo's view, different representations along this continuum are featured by different weightings of somatosensory representations and a visual representation, and therefore distortions can differ in magnitude.

Changes in body shape and size perception can follow after peripheral and central neural changes. For instance, macrosomatognosia has been linked to an increased perception of the hands and face due to migraine aura (Podoll & Robinson, 2000). Gandevia and Phegan (1999) found that subjects, after inducing local anesthesia to the thumb, perceived the thumb to be enlarged by 60-70 percent. This indicates that a lack of tactile efferent information can create the perception of the finger becoming larger. On a slightly different note, patients suffering from complex regional pain syndrome, which involves shrinkage of the primary somatosensory cortex, perceived their affected limb as larger than it actually was as well (Mosely, 2005). Also, other patients with preserved peripheral senses, such as anorexia nervosa, can show disturbances in tactile size perception (Keizer et al., 2011, Keizer et al., 2012, Spitoni et al., 2015). All these studies reveal that body part size perceptions can be disturbed due to both peripheral and central changes.

In short, under certain circumstances we perceive our body as highly distorted, that is, different representations along a continuum are featured by different weightings of somatosensory representations and a visual representation, and therefore distortions can differ in magnitude. There is some evidence that disturbances in how we perceive our body seem to stem from both central and peripheral changes.

Body ownership

The same senses (e.g., vision, proprioception, touch) give us information that our body belongs to us (Azañón, Tamè, Maravita, Linkenauger, Ferrè, Tajadura-Jiménez, & Longo, 2016). For instance, we can continuously see our body, we can feel touch through mechanoreceptors on our body, and we get feedback about the joint angle, muscle tension and muscle length regarding the location of our limbs in space. Also, the brain has access to nociception, interoceptive and vestibular information about our body. For instance, I can differentiate between my hand holding a cup of coffee instead of my friend's hand holding a similar cup, because the multisensory information converges into one single source 'Me': I *see* that I touch the cup of coffee, I *feel* the texture of the cup on my hand, and I sense pain in my hand because the content is too warm. Although I see my friend holding a similar cup, I do not feel the same somatosensations I just mentioned. So, these differences in sensory input allow us to differentiate between what is mine, and what is not mine. Thus, the integration of these senses, i.e., vision, touch and proprioception, contributes to creating awareness of our body and gives us the feeling that our body belongs to us, which is commonly referred to as body ownership (Gallagher, 2000). Considering these physical constraints, body ownership -illusions offer us a way to examine and manipulate the temporal, spatial and semantic features of multisensory processing that gives rise to body ownership. In this thesis I will mainly focus on the temporal and spatial characteristics of multisensory integration.

One of the most studied illusions in body ownership is the Rubber Hand Illusion (RHI). In this illusion, participants see a rubber hand being stroked, while simultaneously the occluded real hand is being stroked. As a result, the participants refer their tactile sensations to the rubber hand (Botvinick & Cohen, 1998). In other words, participants have the illusionary experience that they can feel the touch they visually perceive on the rubber hand. The tactile, proprioceptive and visual information are integrated into a single experience. And when this multisensory input is congruent with (higher order) internal models of the body, participants have the impression that the rubber hand becomes part of their own body (Valenzuela Moguillansky, O'Regan, & Petitmengin, 2013). See Figure 3 for the set-up.

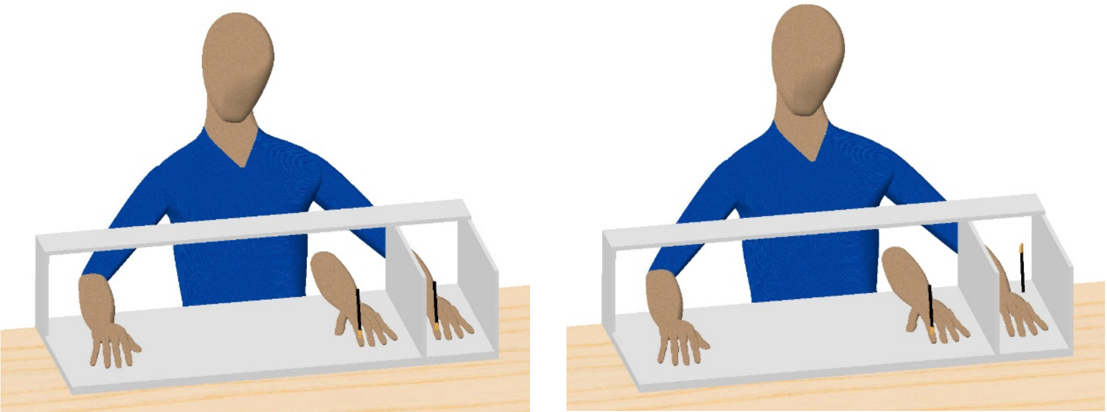

Figure 3. Classic rubber hand illusion set-up. Left: synchronous stroking condition and right: asynchronous stroking condition. See text for details.

The temporal aspect as well as the spatial aspect of the stroking is important, that is, simultaneous strokes (close in time) on homologues regions (close in space) of the rubber hand and the real hand typically make participants more susceptible to experience of the illusion, whereas asynchronous stroking typically results in a less vivid illusionary experience (Botvinick and Cohen, 1998). Next to spatial and temporal features, semantic and structural features are important, such as knowing what our body looks like in terms of shape and anatomic plausibility. The illusion is less likely to occur when the shape of the artificial hand is a wooden block (Tsakiris, 2010) and when the rubber hand is rotated in an anatomically implausible position (Ide, 2013). This indicates that the artificial hand must meet the features of a body specific body model (Tsakiris et al., 2007; Longo et al., 2009; Tsakiris, 2010). When subjects experience the hand as their own, they usually have higher ratings on the embodiment questionnaire, which asks about details of the experience and sensations of the illusion. Another way to measure the magnitude of the illusion is to instruct the participant to estimate where their own occluded hand is located. After the illusion, individuals' estimation usually 'drifts' from their own hand toward the rubber hand, a phenomenon known as proprioceptive drift (e.g., Botvinick and Cohen, 1998; Tsakiris and Haggard, 2005). Other measures have also been used to measure the strength of the illusion, such as skin conductance responses, and temperature (Moseley et al., 2008) (for the latter see a recent meta-analysis conducted by our lab that did not find consistent changes in skin temperature; de Haan et al., 2017). Even when the fake hand is under threat, our body can elicit autonomic responses (Armel and Ramachandran, 2003) to the same extent as if our actual hand was under threat. This shows how powerful this illusion is.

The fact that we usually have ownership about our limbs may not be as self-evident as it seems. In order to experience ownership over our limbs we should be aware of the sensations we feel, in other words we have some bodily awareness over somatosensory and motor sensations. Damage to the parietal cortex can result in either lacking awareness of the sensory deficit of the limb or underestimating the severity of the deficit, the former is called anosognosia and the latter is called anosodiaphoria. Anosognosia is relatively common and occurs in 32% of right hemisphere stroke patents (Vocat, Staub, Stroppini, & Vuillemier, 2010). These disorders typically manifest to the contralesional side of the body. Patients with asomatognosia experience that the affected limb is missing, and patients suffering from somatoparaphrenia misidentify, misrefer to their limb. Patients with misoplegia are often hostile towards the limb and display hatred towards the affected limb (Vallar, 2009; van Stralen, van Zandvoort & Dijkerman, 2011).

From body to bodily space

So far, I have discussed processes concerning the body. Our body is tightly linked to the near (arm length) space around us. We use our hands to interact with the world around us (for instance to pick up that cup of coffee that has been mentioned before). This region surrounding our body is called the peripersonal space (PPS). The PPS is essential for bodily protection and goal directed action (Holmes and Spence, 2004; Ladavas, di Pellegrino, Farne, & Zeloni, 1998, Cooke and Graziano, 2004). The behavioral proxy of PPS is typically measured in detection paradigms (e.g., reaction times in response to a tactile stimulus while simultaneously an approaching visual stimulus is shown) and evidence suggests that the PPS is anchored to one's own body (Serino, Noel, Galli, Canzoneri, Marmaroli, Lissek, & Blanke, 2015). This anchoring is also supported by neurophysiological studies; receptive fields of neurons are centered on head, torso, (see Holmes and Spence (2004) for a review; Ladavas, Zeloni & Farne, 1998) and hands (Graziano & Gross, 1997). These neurons were often bimodal and coded for both tactile and visual information near and on the body. In other words, neurons in these multisensory brain areas respond to a visual stimulus that enters one's PPS (without touch) in the same way as when one is actually being touched. For instance, visual attention facilitated reaction times when it was directed towards a vibration on the skin (i.e., a 'tactile' target) (Driver & Spence, 1998; Macaluso & Maravita, 2010). Likewise, Kandula, Hofman & Dijkerman (2015) revealed that reaction times were shorter when a hand pointed towards the cheek and was followed by a tactile vibration on that cheek as opposed to that hand pointed away from the cheek. Cléry et al., (2015[a]) found similar results of enhanced tactile sensitivity with looming stimuli passing the face. These results suggest a visuo-tactile predictive mechanism; expectation of touch in PPS yields faster responses (see review Cléry et al., 2015[b]). Moreover, Cléry, Guipponi, Odouard, Pinede, Wardak, & Ben Hamed (2017) propose that the spatial and temporal dynamics of PPS can be observed in the same neural networks as multisensory integration. Converging neural evidence (Grivaz, Blanke, & Serino 2017) shows overlapping brain areas for body ownership and PPS, implying they may activate the same mechanism.

Neglecting peri- or extra personal space and its links to somatosensory processing

Other evidence for a link between spatial (either near or far space) representations and the somatosensory processing comes from patients with visuospatial neglect. Unilateral inattention for space can happen after right hemisperic stroke. Usually, after right hemispheric stroke (specifically the right temporo-parietal junction), patients suffering from neglect do not attend to, respond to, and mostly ignore information at the contralesional side of space (usually ignoring the left side following right hemispheric damage) (Vallar, 1997). Vallar raised the idea that anosognosia for left-sided motor and sensory deficits and motor neglect coincides with spatial neglect, indicating a close relationship between lateralized problems regarding the body and space. Vallar (1997) proposed that left-sided (somato)sensory problems may be the resultant of two, additive factors. The first is a primary sensory component as viewed in traditional neurology and describes the contralateral architecture of deficits (i.e., left somatosensory problems after right hemispheric damage and vice versa), and the second one refers to a higher order deficit (e.g., such as visuopatial neglect) which is mainly confined to the right hemisphere, which increases the incidence, the severity, of left-sided somatosensory deficits. Support for this hypothesis comes from studies where they used vestibular stimulation, transcutaneous electrical nervous stimulation of the left neck (Vallar, Rusconi, Bernardini, 1996), optokinetic stimulation (Vallar, Antonucci, Guariglia, & Pizzamiglio, 1993; Vallar, Guariglia, Magnotti, & Pizzamiglio, 1995) and vestibular stimulation which improved spatial neglect (Rubens, 1985) as well as somatosensory problems (Vallar, Sterzi, Bottini, Cappa, & Rusconi, 1990).

Thesis outline

So far, I have discussed the somatosensory system, and higher order body representational and spatial interactions. In my thesis, I aim to investigate how and to what extent primary sensory input can influence these higher order representations. If primary sensory input does modulate these representations, what are the implications for patient groups where primary sensory input is compromised through brain damage? My thesis will address this aim in two parts. In the first part I focus on body and space related interactions in healthy individuals, in the second part I will focus on the same interactions in patients.

For the first part, in healthy controls, I first would like to gain a basic understanding of whether hand ownership is experienced differently for the left and right hand, and whether handedness has a differential impact on that experience. In other words, is body ownership lateralized? Then, I will take it a step further and address whether we need actual tactile input to experience hand ownership. In previous sections, I have discussed the hand distortions extensively, and my question is whether we can change the perceived hand by modulating sensory input. My next question is whether changes in the body representation can transiently alter how we perceive the space around that body part. Answers to these sub questions will offer us insight whether modulations of primary (multi)sensory input can influence higher order body and space representations in healthy individuals. In the second part, I would like to put results found in healthy controls to the test, that is, I would like to gain insight in what happens when actual sensory information is compromised, for instance after stroke. Does diminished afferent input influence higher order representations? Specifically, I ask the question whether intact somatosensation is a necessity to obtain information about body dimensions. And does the absence of these afferent signals modulate hand ownership? In this part I also will present a case who is reporting higher order bodily problems, i.e., complete lack of body ownership, despite having intact afferent signals. Here, I question whether I can modulate the multisensory signals to alleviate his problems. In the final section I question whether repeated appliance of transcranial direct current stimulation to the parietal cortex will alleviate symptoms of spatial neglect. Answers to these questions will offer insight whether multisensory input is a necessity to obtain information about body dimensions, and whether it influences hand ownership. Moreover, in the last two chapters I attempt to alleviate problems in body and space representation with different types of experimental treatment.

1. BODY AND SPACE RELATED INTERACTIONS IN HEALTHY INDIVIDUALS

In **chapter 2** I will investigate whether experiences of ownership are differentiated by handedness and differences between the left and right hand. Body ownership has mainly been linked to the right hemisphere and larger interhemispheric connectivity has been shown to be associated with greater right hemispheric activation. Mixed handed participants tend to have more interhemispheric connectivity compared to extreme handed participants (Gutwinski et al., 2011). The aim of this study is to examine whether the subjective experience of ownership and proprioceptive drift as assessed with the rubber hand illusion (RHI) are differentiated by handedness and differs between the left and right hand. Sinistrals, dextrals, and mixed handed individuals (n=63) are subjected to the RHI. Stroking will be performed synchronously and asynchronously on both the participant's hand and a rubber hand.

In **chapter 3** I investigate the mere expectation of touch and body ownership. Ferri et al., (2013) found, using a variant on the rubber hand illusion, that sense of ownership was evident by mere expectation of touch. Here we aim to further investigate this finding, by studying whether the mere potential for touch yields a sense of ownership similar in magnitude to that resulting from actually being touched. In the first experiment we will utilize the classical rubber hand illusion set-up (Botvinick and Cohen) in 63 healthy individuals, they will perform the following conditions: a synchronous condition, an asynchronous condition, an approached but not touched condition (potential for touch), and a 'visual only' condition. To account for set-up differences, we will use the vertical set-up similar to that of Ferri's in the second experiment using the same stroking conditions. Here we will investigate whether alignment between the real and the rubber hand is able to differentially impact sense of ownership.

In **chapter 4** I investigate whether different gradations of body ownership will be able to change the perception of space around the hand. Peripersonal space (PPS), the region immediately surrounding the body is essential for bodily protection and goal directed action. Since the PPS is anchored to one's own body, I investigate whether the PPS could be modulated by changes in perceived body ownership. The rubber hand illusion (RHI) is a way to manipulate body ownership. I hypothesize that after induction of a left-handed RHI, the perceived space around the body shifts to the right. Sixty-five participants will perform a landmark task *before* and *after* a left-handed RHI. In the landmark task, participants have to determine whether a landmark was left or right from the center of a horizontal screen. One group of the participants will be exposed to synchronous stroking, the other group will experience asynchronous stroking. I am interested whether the induction of the rubber hand illusion will differentially (i.e., synchronous vs. asynchronous stroking) cause a shift in the landmark judgements between pre-and post-testing.

In **chapter 5**, I investigate how we perceive our hands under different sensory circumstances. Research has shown that the perceived representation of the hands is highly distorted, featuring shortened fingers and broadened hands. This pattern of distortion matches the geometry and tactile acuity of the receptive field on the dorsal side of the hand. The degree of distortions appears to depend on the sensory information available. My aim is to test whether the perceived hand representation can be differentially modulated, i.e., I will examine the sensory contributions of different afferent signals (proprioception, touch, movement) to the implicit hand representation. Twenty-three healthy individuals will participate in this study. An adapted version of a body localization task will be administered to induce an implicit representation of the hand. Sensory signals will be manipulated in four different conditions: a proprioceptive condition (hand still under monitor), a touch condition (i.e., touch on finger), a movement condition (i.e., movement of finger), and an imagine condition (i.e., absence of the hand).

2. BODY AND SPACE RELATED INTERACTIONS IN PATIENTS

Research shows that the somatosensory system plays an important role in both body representation (BR) and PPS. The study in **chapter 6** aims to examine the effect of long-term somatosensory loss in the hand on the metric features of the BR, by including patients with somatosensory loss due to stroke and healthy age-matched controls. Two types of representations will be examined in both hands; a more visual, explicit BR and a more somatosensory, implicit BR. In total 21 healthy controls and 13 patients will be included.

In **chapter 7** I present an individual displaying ownership problems without primary sensory impairments. Reports on patients who lack ownership over their entire body are extremely rare. The presented patient suffers from complete body disownership after a tumor resection in the right temporo-parietal cortex. I will administer neuropsychological assessment and assess the effect of multisensory retraining on body ownership.

In **chapter 8** I investigate a stimulation technique in order to treat hemispatial neglect. Prior research suggests that dampening neural activity of the intact, presumably overactive hemisphere, combined with increasing neural activity in the damaged hemisphere, might restore cortical interhemispheric balance and reduce neglect. In the present study I will repeatedly apply a relatively new technique, transcranial direct current stimulation (tDCS), to the posterior parietal cortex to modulate spontaneous neural activity levels in a polarity dependent fashion to find evidence for improvements in severe hemispatial neglect in chronic patients. Eighty-nine patients will be considered for a double-blind, placebo-controlled treatment program. TDCS or placebo will be applied for 20 minutes over the left (cathodal) and right (anodal) posterior parietal cortex at an intensity of 2 mA on five consecutive days. Treatment conditions will be separated by a four-week wash-out period. Baseline corrected change in performance on the conventional subtests of the Behavioural Inattention Test (BIT) is my primary endpoint.

In **chapter 9** I will conclude the thesis with a general discussion.

Chapter 2

Laterality and Body Ownership: Effect of Handedness on Experience of the Rubber Hand Illusion

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Published in: Laterality, 2017

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ABSTRACT

Body ownership has mainly been linked to the right hemisphere and larger interhemispheric connectivity has been shown to be associated with greater right hemispheric activation. Mixed handed participants tend to have more interhemispheric connectivity compared to extreme handed participants. The aim of this study was to examine whether feelings of ownership as assessed with the rubber hand illusion (RHI) are differentiated by handedness and differed between the left and right hand.

Sinistrals, dextrals, and mixed handed individuals (n=63) were subjected to the RHI. Stroking was synchronously and asynchronously performed on both the participant's hand and a rubber hand. Outcome measures were an embodiment questionnaire and proprioceptive drift. In contrast to our hypotheses we show a similar experience of ownership for all groups, which may indicate no hemispheric specialization for the illusion. In addition, plasticity of ownership and body ownership are similar for the left hand and right hand in all participants, which suggests similar representations for both hands in the brain. This might be useful to maintain a coherent sense of the body in space.

INTRODUCTION

When someone points at your hand and asks if that hand belongs to you, you will immediately confirm that it is your hand. But how do we know that our hand actually belongs to our body? This may not be as self-evident as it appears. Indeed, body ownership can be experimentally manipulated and therefore examined with for example the well-known rubber hand illusion (RHI). In this illusion, participants see a rubber hand being stroked, while simultaneously the occluded real hand is being stroked. As a result, the participants refer their tactile sensations to the rubber hand (Botvinick & Cohen, 1998). In other words, participants have the illusionary experience that they can feel the touch they visually perceive on the rubber hand. The tactile, proprioceptive and visual information are integrated into a single experience. And when this multisensory input is congruent to internal models of the body, participants have the impression that the rubber hand becomes part of their own body (Valenzuela Moguillansky, O'Regan, & Petitmengin, 2013).

Previous studies suggest a strong link between the right hemisphere and awareness of the subjective experience of body ownership (e.g. Frasinetti, Maini, Romualdi, Galante, & Avanzi, 2008; Karnath & Baier, 2010; Tsakiris, Hesse, Boy, Haggard, & Fink, 2007; Vallar & Ronchi, 2009). More specifically, brain areas involved in body ownership include the right temporoparietal junction (Tsakiris, Constantini, & Haggard, 2008), the secondary somatosensory cortex (Press, Heyes, Haggard, & Eimer, 2008), the posterior parietal and ventral premotor cortices (Ehrsson, Spence, & Passingham, 2004; Zeller, Gross, Bartsch, Johansen-Berg, & Classen, 2011), and the right posterior insula (Karnath & Baier, 2010). This is further supported by the right lateralization of brain lesions that typically lead to somatoparaphrenia (misidentification and confabulation of limbs) (Vallar & Ronchi, 2009).

Research with split-brain patients has shown that feelings of ownership depend on interhemispheric communication, specifically in the posterior corpus callosum (Uddin, 2011). Interestingly, interhemispheric connectivity appears to vary with handedness. Studies have revealed that the corpus callosum of sinistrals tends to be larger than the corpus callosum of dextrals, which suggests greater interhemispheric connectivity in sinistrals (Gutwinski et al., 2011). This is particularly relevant, since one's percept of one's own body may entail cross-talk between the two hemispheres. The left hemisphere has been suggested (Ramachandran, Rogers-Ramachandran, & Cobb, 1995; Ramachandran & Blakeslee, 1998) to serve as a belief maintenance system in an ever-changing world, while the right hemisphere updates and evaluates these beliefs, i.e., detects anomalies. This may also have implications for body representations. Research by Hach and Schütz-Bosbach (2010) concerning representation of one's own body space suggested that implicit body representation differences (e.g., indicate stimuli on one's left and right body midline with eyes closed) are linked to a stronger lateralization or greater activation imbalance in dextrals. In contrast, sinistrals have greater access to right hemispheric functions, such as an 'up to date' body representation following synchronized visuotactile input. As a consequence they might experience ownership over a fake hand to a greater extent (Hach & Schütz-Bosbach, 2010).

However, other studies show that body ownership may not depend on the direction (whether one is left or right handed), but on the degree of handedness. Niebauer, Aselage, and Schutte (2002) found that mixed handed participants are more receptive to ownership of a rubber hand than extreme handed participants. Their results indicated that, when strength of handedness increased, scores on the illusion scale decreased in the left hand RHI. In their second experiment, participants had to say "now" when, during stroking, participants experienced touch coming from the rubber hand or when participants felt the fake hand becoming part of their body. Time to experience these feelings of ownership increased when (absolute) laterality quotients increased (Niebauer et al., 2002). Christman, Henning, Geers, Propper, and Niebauer (2008) and Prichard, Propper, and Christman (2013), support this line of reasoning, and suggest that mixed handed individuals have greater interhemispheric connectivity than extreme handed individuals. Moreover, research by Luders et al., (2010) showed a negative association between callosal size and handedness lateralization in which extreme handedness was associated with smaller corpus callosum size. Interestingly, when extreme handed participants were compared with mixed handed participants, a decrease in right hemisphere activation was found (Propper, Pierce, Geisler, Christman & Bellorado, 2012). As body ownership appears to be right lateralized, this may suggest that mixed handed participants have a better-developed sense of body ownership. In the current study we tested this hypothesis by applying the rubber hand illusion (RHI) to participants with varying degrees of left or right handedness. Since handedness constitutes a robust proxy for laterality, we aim to test the effect of handedness on the subjective and objective experience of the RHI.

So far, most studies, that investigated the RHI, tested dextrals with a left rubber hand (e.g., Botvinick & Cohen, 1998; Haggard & Jundi, 2009; Tsakiris & Haggard, 2005) or a right rubber hand (e.g. Armel & Ramachandran, 2003; Constantini & Haggard, 2007; Kammers, de Vignemont, Verhagen, & Dijkerman, 2009; Lloyd, 2007; Shimada, Fukuda, & Hiraki, 2009). A few studies used both hands but did not statistically compare the hands (e.g., Pavani, Spence, & Driver, 2000; Walton & Spence, 2004). Mussap and Salton (2006) did compare the hands, but did not find a subjective (using an embodiment questionnaire) difference between the left and right hand. Interestingly, Michael et al. (2012) found that particularly dextrals are more receptive to spontaneous sensations (e.g., beat/pulse, tickle) for their left hand as opposed to their right hand.

With respect to handedness, so far, only a few studies, incorporated a few sinistrals (e.g., IJsselsteijn, de Kort, & Haans, 2006; Haans, IJsselsteijn, & de Kort 2008; Constantini & Haggard, 2007; Rohde, Di Luca, & Ernst, 2011) and only Haans et al. (2008) tested whether handedness influenced experience of the RHI. They reported no difference in experience between sinistrals and dextrals. However, this might be due to a lack of statistical power, since 18 of the 23 participants were right handed and thus the number of sinistrals was very small. To date, only Ocklenburg, Rüther, Peterburs, Pinnow, and Güntürkün (2011) systematically explored whether sinistrals and dextrals differed in experience of the RHI. Experience of the illusion was measured with skin conductance responses (SCR) and an embodiment questionnaire. The SCR was stronger for the left hand, while there was no difference between sinistrals and dextrals when experience of the illusion was objectively measured. Taken together, the right hemisphere, linked to the somatosensory and visual signals from the left side of the body, as opposed to the left hemisphere, seems to update at a faster rate. This is consistent with the enhanced spontaneous sensations for the left hand (Michael et al., 2012) and susceptibility of the RHI for the left hand (Ocklenburg et al., 2011).

In order to decipher inconsistencies regarding laterality (extreme versus mixed) and the hand used (left vs right) in the sense of ownership, we systematically examine differences in sense of ownership between sinistrals, dextrals and mixed handed individuals, by using relatively large groups. In addition to the classic subjective (embodiment) questionnaires we also use an established objective measure of the RHI, i.e., proprioceptive drift instead of using skin conductance, the latter being used in Ocklenburg et al., 2011). We also use stringent handedness quotients; participants were considered sinistral if the laterality quotient, according to the *Edinburgh Handedness Inventory:* The EHI (Oldfield, 1971), was below -80, mixed handed if the laterality quotient was between -80 and 80 and dextral if the laterality quotient was above 80. It is important to note that Ocklenburg et al., (2011) differentiated sinistral and dextral as smaller or larger than zero. Niebauer et al., (2002) however found a correlation between ownership over the rubber hand and handedness, but did not specify the average EHI score in their study. Based on previous research we hypothesize a different experience of the RHI for the different handedness groups. We specifically expect differences in experience of the RHI on both the objective and subjective measures for mixed handed participants as opposed compared to extreme handed (extreme sinistrals and dextrals). In addition, we expected a higher degree of ownership for the left hand than for the right hand in all handedness groups.

METHODS

Participants

Sixty-three individuals participated. The individuals were screened online prior to participation. Online questionnaires contained questions regarding demographics (age, sex, education), the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), a screening for history of neurological/psychiatric disorders and substance abuse. Participants who reported either a history of neurological/psychiatric disorders or substance abuse were excluded from participation. Participant demographics are shown in Table 1. Based on laterality quotients calculated for the EHI (for the equation, see below, materials), 21 participants were assigned to either the group of sinistrals, mixed handed participants and dextrals. As stated by Hardie and Wright (2014), a majority of laterality studies use a notional median of 80 (e.g., Jasper et al., 2008; Christman and Butler, 2011; Lyle and Orsborn, 2011; Westfall et al., 2012). Therefore, participants were considered extreme handed if the laterality quotient was below -80 (sinistrals) or above 80 (dextrals) and mixed handed if the laterality quotient was between -80 and 80. Additionally, in order to make comparisons across former studies possible Ocklenburg et al., (2011) we also calculated a broader, hence more liberal division between left- and right handed individuals; laterality quotients between -1 and -100 are considered left-handed individuals and laterality quotients ranging from 1 till 100 are considered right handed individuals. Prior to the experiment informed consent was obtained and the nature of the study was clarified. Each participant received course credit or 6 euros.

Table 1. *Mean Age and SD (standard deviation), Gender and mean Laterality Quotients and SD (as assessed with the EHI (Oldfield, 1971)) for Handedness Groups and Total.*

	Age		Gender		Laterality Quotient[a]	
	M	*SD*	Male	Female	*M*	*SD*
Left-handed (n=31)	23.30	(3.66)	12	19	-81.90	(24.14)
Right-handed (n=31)	23.06	(4.34)	12	19	84.46	(17.35)
Extreme handed (n=42)	22.64	(3.31)	14	27	-.42[b]	(91.11)
Mixed handed (n=21)	24.00	(4.97)	9	12	4.62	(61.79)
Total	23.10	(3.95)	24	39	1.26	(85.71)

[a]Range laterality quotients: Left-handed between -1 and -100; Right-handed between 1 and 100; Extreme handed include sinistrals between -80 and -100 and dextrals between 80 and 100; Mixed handed between -79 and 79. [b]Note that the extreme handed individuals consist of sinistrals (average LQ = -95.10; SD =7.40) and dextrals (average LQ = 94.25; SD =7.57).

Design

A within-subjects design was used in which all participants completed four stroking conditions twice, resulting in 8 trials in total. The four conditions, as shown in Figure 1, were synchronous left hand stroking, asynchronous left hand stroking, synchronous right hand stroking and asynchronous right hand stroking. Block order was pseudorandomized; four trials for one hand (two synchronous, and two asynchronous, see Figure 1) were performed before stroking was performed on the other hand. Then, asynchronous stroking in one hand was always followed by synchronous stroking. At random, the experiment started with synchronous or asynchronous stroking of either the left or right hand. The fifth trial, subsequently, started at random with synchronous or asynchronous stroking of the other hand.

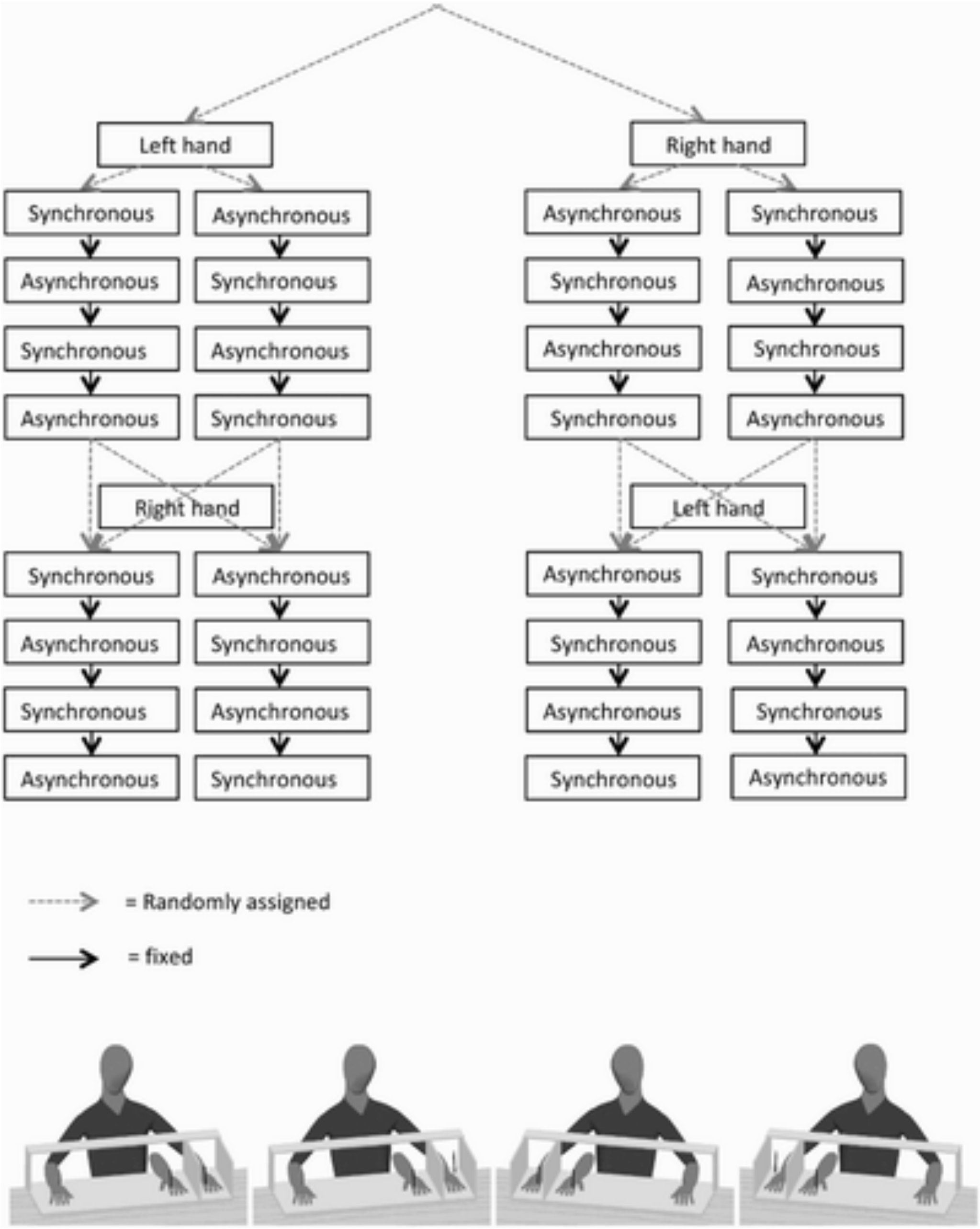

Figure 1. Top: Block order of stroking (i.e., synchronous, asynchronous) conditions for both hands, and bottom: experimental set-up of all stroking conditions, from left to right: left synchronous stroking, left asynchronous stroking, right synchronous stroking and right asynchronous stroking.

Procedure/Task/Stimuli

Procedure

All measurements were conducted in a quiet lab at Utrecht University, and participants were seated comfortably. Participants received a brief verbal explanation and signed informed consent prior to the experiment. All trials consisted of measuring proprioceptive drift, inducing the RHI, measuring proprioceptive drift, and filling out the embodiment questionnaire, respectively.

Questionnaire: Edinburgh Handedness Inventory: The EHI (Oldfield, 1971) consists of ten items for which the participant is instructed to place a checkmark which hand is preferred. If there is such a strong preference that the other hand would never be used, the participant is instructed to place two checkmarks. Laterality quotients were calculated with the following formula.

$$LQ = \frac{R - L}{R + L} \times 100$$

LQ stands for Laterality Quotient, L is the sum of checkmarks for the left hand and R is the sum of checkmarks for the right hand.

RHI: Participants were seated at a table. The arm of their stimulated hand and the arm of the rubber hand were covered with a black cloth. The cloth prevented the participant to see the proximal end of the rubber hand. As shown in Figure 1, the rubber hand and the hands of the participant were placed on a fixed (marked) location within a wooden framework (79 cm in width, see Figure 2 for exact dimensions). The space between the stimulated own hand and the RH was approximately 17 cm. In the framework, there is a compartment for the hidden stimulated hand (outer compartments) and a compartment for the rubber hand and the unstimulated hand (inner compartment). The positions of the hands were similar for all stroking conditions and for each hand. The participant's real hand was placed, depending on which hand was stroked, in the outer compartment (see Figure 2) of the box. The center of the wrist was placed on the red marks, and the rubber hand was always on the same position on one of the red dots (depending on which hand was being stroked) in the inner compartment. When measuring proprioception (before and after illusion) a wooden lid was placed on top of the box.

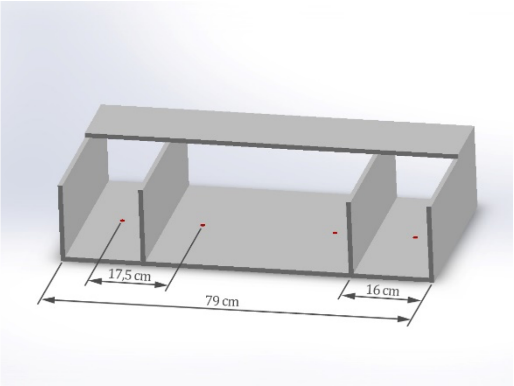

Figure 2. Experimental set-up and exact dimensions, see text for details.

Stroking procedure: During the 90 sec illusion, both the unstimulated hand and the rubber hand were visible for the participant. Two identical brushes were used to stroke the rubber and the real hidden hand. Stroking was performed from knuckle to fingertip. Outcome measures were embodiment questionnaire and proprioceptive drift and will be discussed shortly. In the synchronous conditions, the experimenter stroked the rubber hand and the real hand of the participant synchronously. More specifically, we performed similar but irregular stroke frequencies varying from one stroke per second and one stroke per three seconds. In the asynchronous condition, the rubber hand and the real hand were stroked sequentially in a similar pattern. As such the brush only touched one hand at a time (either the rubber hand or the real hand). In the left hand conditions, the real left hand of the participant and the left rubber hand were stroked and vice versa for the right hand conditions. Positioning of the hands of the participants was similar in all conditions.

*Embodiment questionnaire***.** An embodiment questionnaire was used to measure subjective strength of the illusion (Kammers et al., 2009). The questionnaire consisted of ten statements. Answers were given on a ten point Likert scale, ranging from 1 (*disagree strongly*) to 10 (*agree strongly*). Three of these statements measure the subjective strength of the illusion. These statements are: ‘It seemed as if I were feeling the touch of the paintbrush in the location where I saw the rubber hand touched, it seemed as though the touch I felt was caused by the paintbrush touching the rubber hand and it felt as if the rubber hand were my hand’. The remaining statements are considered control questions (Kammers et al., 2009). Since conditions were induced twice, the average of the conditions was used for analyses. The ten questions were analyzed separately and an average was calculated for the first three questions and the remaining questions for each condition.

Proprioceptive drift:

Proprioceptive drift was measured in millimeters. To assess proprioceptive drift, a cardboard was placed on top of the box (so the participant could not see to see his/her own hands and the rubber hand). The experimenter moved her own index finger alongside the back of the box (random outwards to inwards or vice versa) and the participant was instructed to say *stop* when the index finger of the experimenter matched the location of where the participant felt his/her own index finger. Using a small lead weight (hanging on the index finger of the experimenter) and a tape measure, the location was verified. Proprioception of the stimulated hand was measured first and of the unstimulated hand second. Proprioceptive drift was the difference between the estimated location of the index finger after induction of the RHI and the estimated location of the index finger before induction of the RHI. A positive number denoted a drift towards the rubber hand. All conditions were induced twice; therefore the average proprioceptive drift for each condition was used for analyses. The total duration of the experiment was approximately 70 minutes.

Analyses

Most of our data were not normally distributed. We initially used transformation procedures and outlier removal procedures offered by Field (2013). Transforming the data (log transformation, square root transformation, reciprocal transformation) or removing outliers (trimming data by deleting 10% of the highest or lowest scores or excluding data above or below 2.5 SD or 3.5 SD) did not result in normally distributed data. Therefore we used a 2 (Hand tested; left, right) x 2 (Synchronicity; synchronous, asynchronous) x 2 (Handedness; left-handed, right-handed, x 2 (Handedness strength; extreme, mixed) mixed ANOVA and applied a non-parametric bootstrap over the entire data-set. Robust statistics, such as bootstrap has no assumptions about normality. It is also argued that transforming data (e.g., trimming of outliers) is in this type of analyses no longer necessary. In this analysis we used 'hand tested' (left versus right) and 'synchronicity' (synchronous versus asynchronous) as within subject factors and 'handedness' (left-handers versus right handers) and 'handedness strength' (extreme versus mixed) as between subject factors. In our bootstrap we used 1000 iterations and obtained 95% confidence intervals (CI) of F-values for each statistic and for both outcome measures (i.e., proprioceptive drift and embodiment questionnaire). For readers' convenience we presented 2 different divisions of Laterality Quotients (LQ) in each graph; in the left panel we presented data of the extreme handed (LQ's < -80 (sinistrals) and > 80 (dextrals)) and mixed handed (LQ's between -80 and 80), in the right panel we presented left- (LQ's between -1 and -100) and right-handed (LQ's between 1 and 100)[1] data. RStudio was used for statistical computing and bootstrapping graphics. If not stated otherwise, alpha levels of .05 (two-tailed) were used for the statistical tests.

RESULTS

Hypotheses

We expected the RHI to be stronger for the mixed handed participants than for the extreme handed participants. In addition, we examined whether stroking the left hand resulted in a higher degree of ownership over the rubber hand than stroking the right hand in all handedness groups.

Subjective embodiment of the rubber hand illusion

Questions 1-3 from the embodiment subscale formed the ownership subscale (Kammers et al., 2009) and the higher the average score of this subscale, the more subjective strength of the illusion was experienced.

It was therefore expected that questions 1-3 were scored above 5 (neutral) in the synchronous but below 5 in the asynchronous conditions, for both hands in all groups. As can be seen in Figure 3, and Figure 4, this was the case for both the left and the right hand respectively. This indicates that in general, for all groups, the illusion was successfully induced.

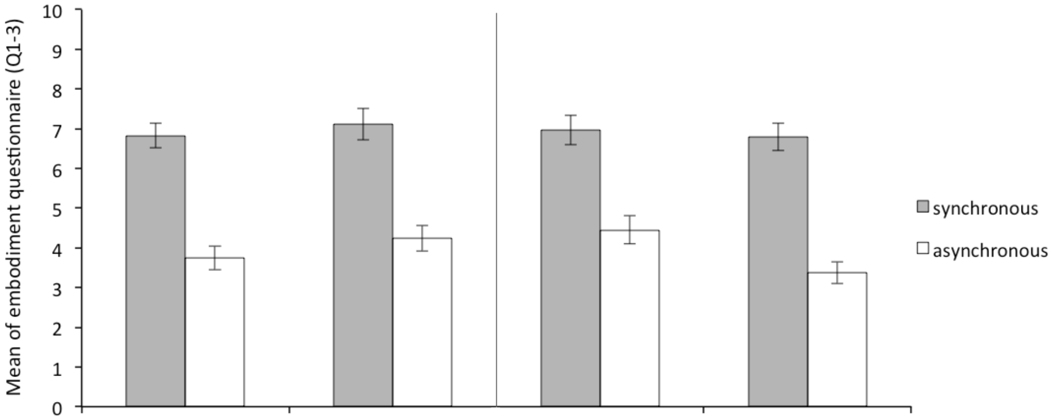

Figure 3. Average of the 'ownership scale' (average Q1-3) of the Embodiment questionnaire for the left hand in the synchronous and asynchronous condition for the extreme- and mixed handed division (left panel) and right-handed and left-handed division (right panel). Error bars represent Standard Error (SE) of the mean.

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[1] One participant was excluded from this division, as the LQ is exact zero.

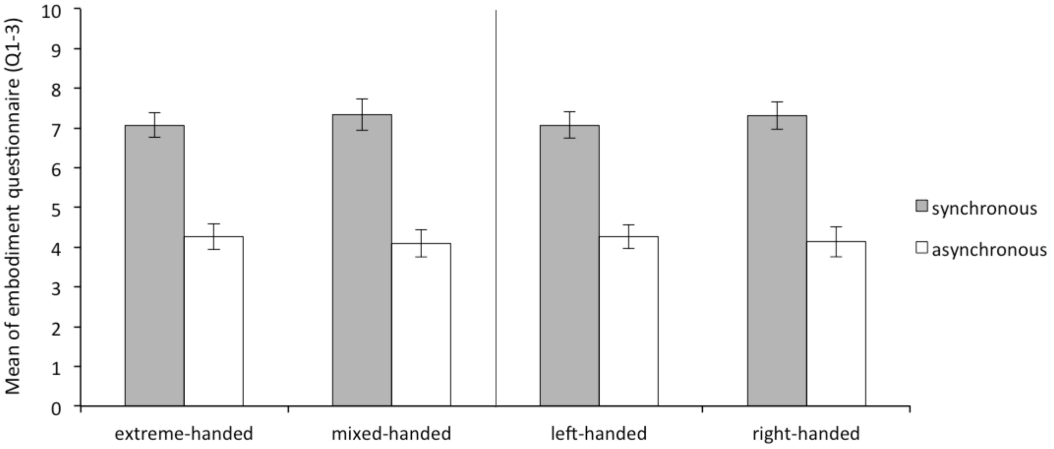

Figure 4. Average of the 'ownership scale' (average Q1-3) of the Embodiment questionnaire for the right hand in the synchronous and asynchronous condition for the extreme- and mixed handed division (left panel) and right-handed and left-handed division (right panel). Error bars represent Standard Error (SE) of the mean.

The remaining questions served as control questions (Kammers et al., 2009). Scores above 5 could indicate that participants were influenced by an 'observer-expectancy' bias. These questions were grouped together on the control subscale (average questions 4-10). The control questions are shown in Figure 5 for the left hand and Figure 6 for the right hand stroking conditions. No difference can be observed between synchronous and asynchronous stroking and for both hands the average ratings were below 5, indicating that it is highly unlikely that the subjective data was influenced by experimenter bias.

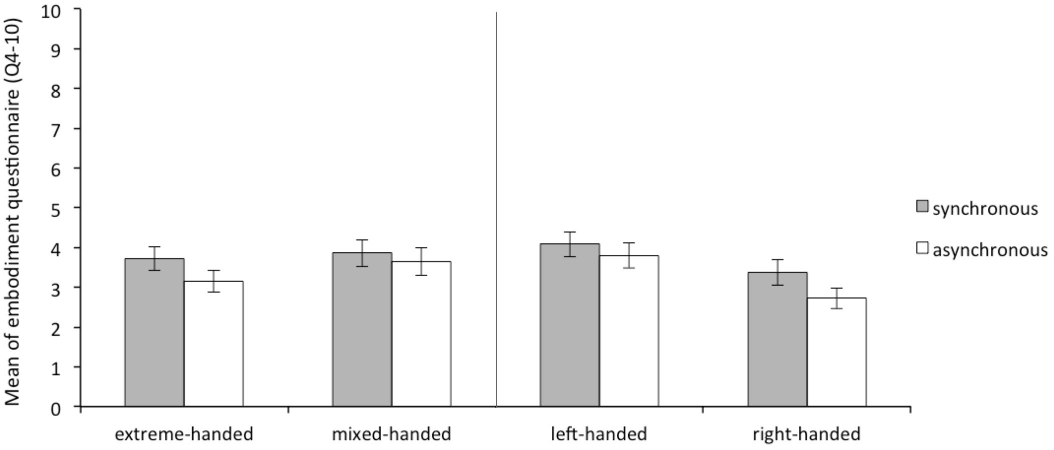

Figure 5. Average of the 'control questions' (average Q4-10) of the Embodiment questionnaire for the left hand in the synchronous and asynchronous condition for the extreme- and mixed handed division (left panel) and right-handed and left-handed division (right panel). Error bars represent Standard Error (SE) of the mean.

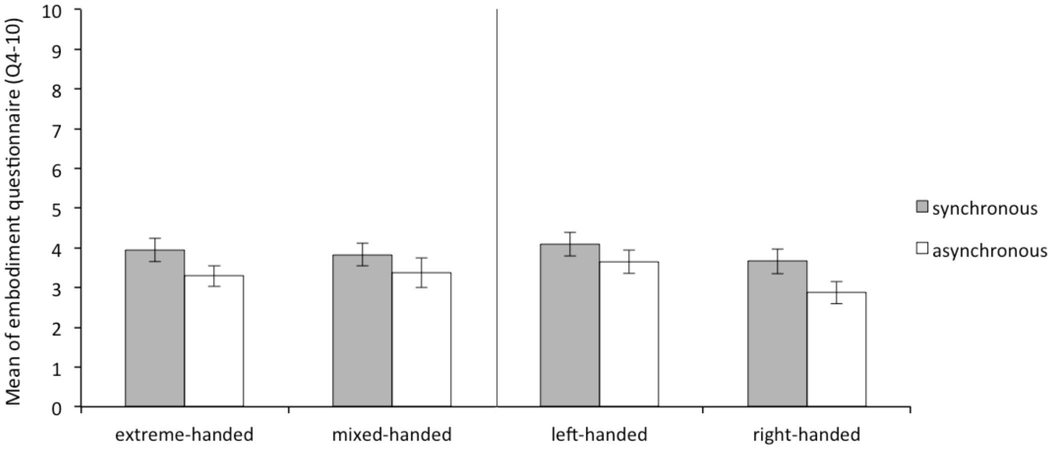

Figure 6. Average of the ‘control questions’ (average Q4-10) of the Embodiment questionnaire for the right hand in the synchronous and asynchronous condition for the extreme- and mixed handed division (left panel) and right-handed and left-handed division (right panel). Error bars represent Standard Error (SE) of the mean.

Taken together, visual inspection of the data suggests that the ownership ratings in the synchronous condition were above neutral (average=5) in all groups, indicating the illusion was successfully induced. No difference can be observed (see Figure 5 and 6) between synchronous and asynchronous stroking across groups for the remaining control questions, and for all groups the mean ratings were below 5. Formal statistical analyses were run on the ownership subscale only.

For ‘synchronicity’, a mixed ANOVA revealed an expected main effect, *F*(1,58) = 118.01, *p* < .001, ηp^2 = .67, indicating that the subjective experience of ownership was stronger in the synchronous than the asynchronous condition. Other main-effects (i.e. ‘hand-tested’, ‘handedness (left vs. right)’, ‘handedness strength’ were not significant, summarized: *F*(1,58) < 1.46, *p* > .232.

Against our expectation, there was no 2-way interaction between ‘hand tested’ and ‘synchronicity’, *F*(1,58) = 0.25, *p* = .618, ηp^2 < .01, indicating that the subjective experience of ownership did not differ between the left and right hand. Next, neither the interaction between ‘handedness strength’ and ‘synchronicity’, *F*(1,58) = 0.04, *p* = .847, ηp^2 < .01, nor the interaction between ‘handedness’ and ‘synchronicity’ was significant *F*(1,58) = 0.45, *p* = .506, ηp^2 = .01. There was a significant 2-way interaction between ‘handedness’ x ‘hand-tested’ *F*(1,58) = 4.08, *p* = .048, ηp^2 = .07. However this effect did not interact with ‘synchronicity’. Other 2-way interactions that did not include the factor ‘synchronicity’ and we had no specific hypotheses about (i.e., 'handedness' x 'handedness strength'; 'handedness strength' x 'hand-tested') were not significant, summarized: $F(1,58) < 1.34$, $p > .252$.

Against our expectations, there was no 3-way interaction between 'hand-tested', 'synchronicity', 'handedness strength', $F(1,58) = 1.24$, $p = .270$, $\eta p^2 = .02$ nor a 3-way interaction between 'hand-tested', 'synchronicity', 'handedness', $F(1,58) = 2.60$, $p = .112$, $\eta p^2 = .04$. The 3-way interaction of 'handedness' x 'handedness strength' x 'hand-tested' was not significant either $F(1,58) = 0.81$, $p = .373$, $\eta p^2 = .01$. Lastly, 'synchronicity' did not interact with 'hand-tested', and different 'handedness groups' (i.e. left vs. right; extreme vs. mixed), $F(1,58) = 1.38$, $p = .244$, $\eta p^2 = .02$.

All in all, analyses indicate that for the subjective embodiment ownership scale 'synchronicity' had no differential impact in either the left or right hand and both handedness groups (i.e. left- and right-handed individuals and, extreme and mixed-handed individuals).

Hereafter we applied a non-parametric bootstrap with 1000 iterations. We then plotted (see Figure 7) the 95% confidence intervals (CI) of these F-values for each statistical test. In Figure 7 we see that the 95% CI of F- values for 'synchronicity' (95% CI [127.21 –130.52] not displayed in plot) and for 'handedness x hand tested' exceeded criterion F (≈ 4.01, based on degrees of freedom). The latter effect does not interact with 'synchronicity'. The confidence intervals of other effects did not exceed the critical F, hence after resampling the data 1000 times there is a high level of confidence that the true F for 'handedness' x 'synchronicity' falls below the critical F.

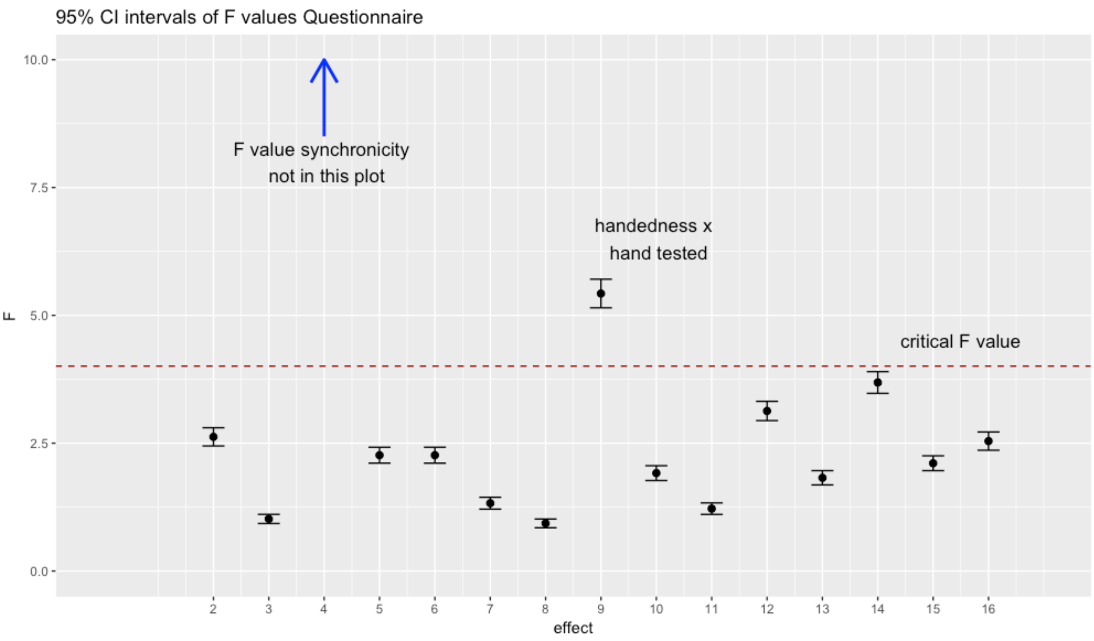

Figure 7. Confidence intervals (95%) of F Values (vertical axis) for each statistical effect (horizontal axis: 2= handedness, 3= strength handedness, 4= synchronicity, 5= hand, 6= handedness x strength handedness, 7= handedness x synchronicity, 8= strength handedness x synchronicity, 9= handedness x hand, 10= strength handedness x hand, 11= synchronicity x hand, 12= handedness x strength handedness x synchronicity, 13= handedness x strength handedness x hand, 14= handedness x synchronicity x hand, 15= strength handedness x synchronicity x hand, 16= handedness x strength handedness x synchronicity x hand). Red dashed lines represents criterion F (≈ 4.01).

Proprioceptive drift

Proprioceptive drift was operationalized as the difference between the estimated location of the index finger before induction of the RHI and the estimated location of the index finger after induction of the RHI**.** A larger value indicates larger shift towards the rubber hand. As expected, synchronous stroking resulted in a larger proprioceptive drift than asynchronous stroking (see Figure 8 and 9) for the left and right hand respectively.

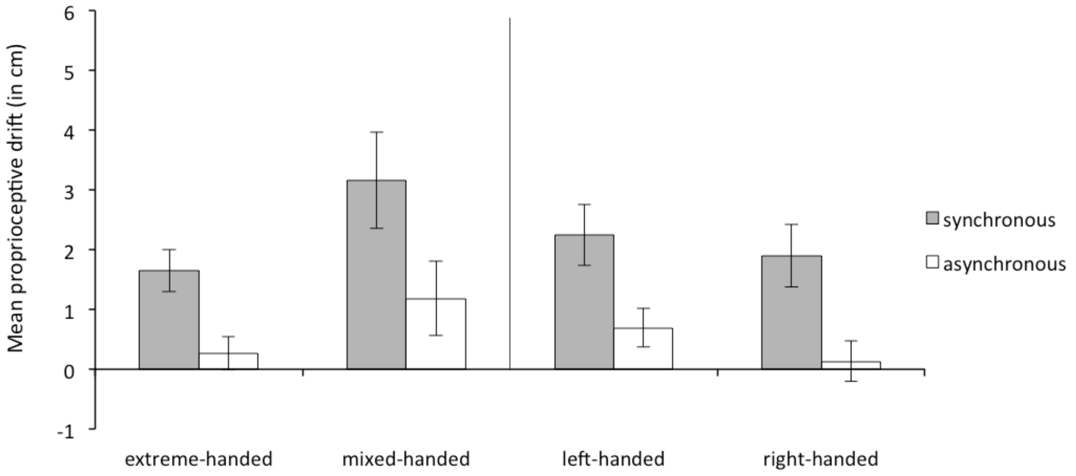

Figure 8. Average proprioceptive drift in the synchronous and asynchronous condition for the left hand for the extreme- and mixed handed division (left panel) and right-handed and left-handed division (right panel). Error bars represent Standard Error (SE) of the mean.

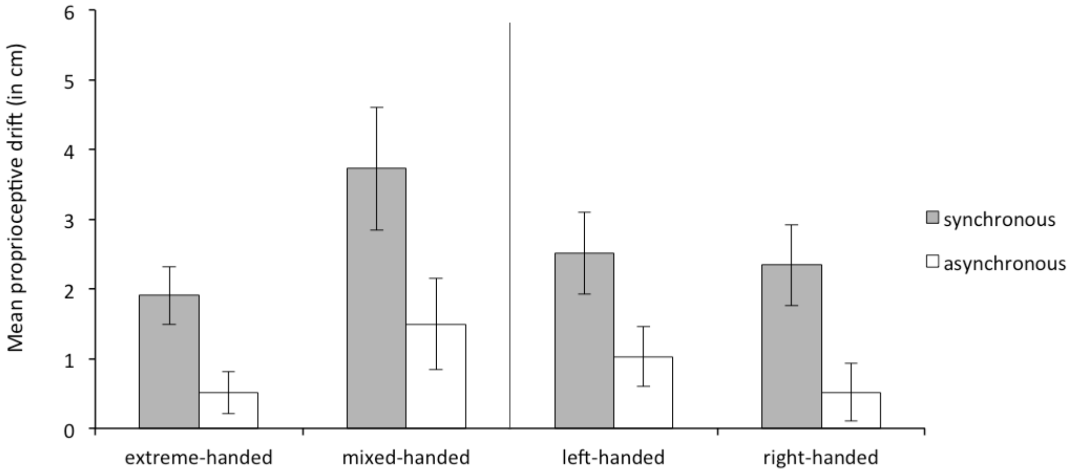

Figure 9. Average proprioceptive drift in the synchronous and asynchronous condition for the right hand for the extreme- and mixed handed division (left panel) and right-handed and left-handed division (right panel). Error bars represent Standard Error (SE) of the mean.

Results for the proprioceptive drift resemble results of the subjective embodiment measurements. For 'synchronicity', a repeated measures ANOVA revealed an expected main effect, $F(1,58) = 37.10$, $p < .001$, $\eta p^2 = .39$, indicating that proprioceptive drift was stronger in the synchronous than the asynchronous condition. Other main-effects (i.e. 'hand-tested', 'handedness (left vs. right)', 'handedness strength' were not significant, summarized: $F(1,58) < 3.89$, $p > .053$.

Against our expectation, there was no 2-way interaction between 'hand tested' and 'synchronicity', $F(1,58) = 0.00$, $p = .993$, $\eta p^2 < .01$, indicating that proprioceptive drift did not differ between the left and right hand. Next, neither the interaction between 'handedness strength' and 'synchronicity', *F*(1,58) = 2.07, *p* = .155, ηp^2 = .03, nor the interaction between 'handedness' and 'synchronicity' was significant *F*(1,58) = 0.26, *p* = .612, ηp^2 < .01. Other 2-way interactions that did not include the factor 'synchronicity' and we had no specific hypotheses about (i.e. 'handedness' x 'handedness strength'; 'handedness' x 'hand-tested'; 'handedness strength' x 'hand-tested') were not significant either, summarized: *F*(1,58) < 0.36, *p* > .550.

Against our expectations, there was no 3-way interaction between 'hand-tested', 'synchronicity', 'handedness strength', *F*(1,58) = 0.01, *p* = .938, ηp^2 < .01, nor a 3-way interaction between 'hand-tested', 'synchronicity', 'handedness', *F*(1,58) = 0.02, *p* = .888, ηp^2 < .01. The 3-way interaction of 'handedness' x 'handedness strength' x 'hand-tested' was not significant either *F*(1,58) = 0.43, *p* = .516, ηp^2 = .01.

Lastly, 'synchronicity' did not interact with 'hand-tested', and different 'handedness groups' (i.e. left vs. right; extreme vs. mixed), *F*(1,58) = 0.48, *p* = .491, ηp^2 = .01.

Taken together, analyses indicate that for the outcome measure proprioceptive drift the type of stroking had no differential impact in either the left or right hand and both handedness groups (i.e. left- and right-handed individuals and, extreme and mixed-handed individuals).

Again, after bootstrapping (1000 iterations) the entire data set for our outcome measure proprioceptive drift (see Fig. 10), only the confidence intervals for the effects of 'strength handedness' (mixed vs extreme) and 'synchronicity' (95% CI [42.96 – 44.96] not displayed in Fig. 10) exceeded criterion F (≈ 4.01, based on degrees of freedom). Interaction-effects including 'synchronicity' did not exceed criterion F. This indicates that after numerous replications there is a high level of confidence that type of stroking (synchronicity) had no differential impact in either the left or right hand and both handedness groups.

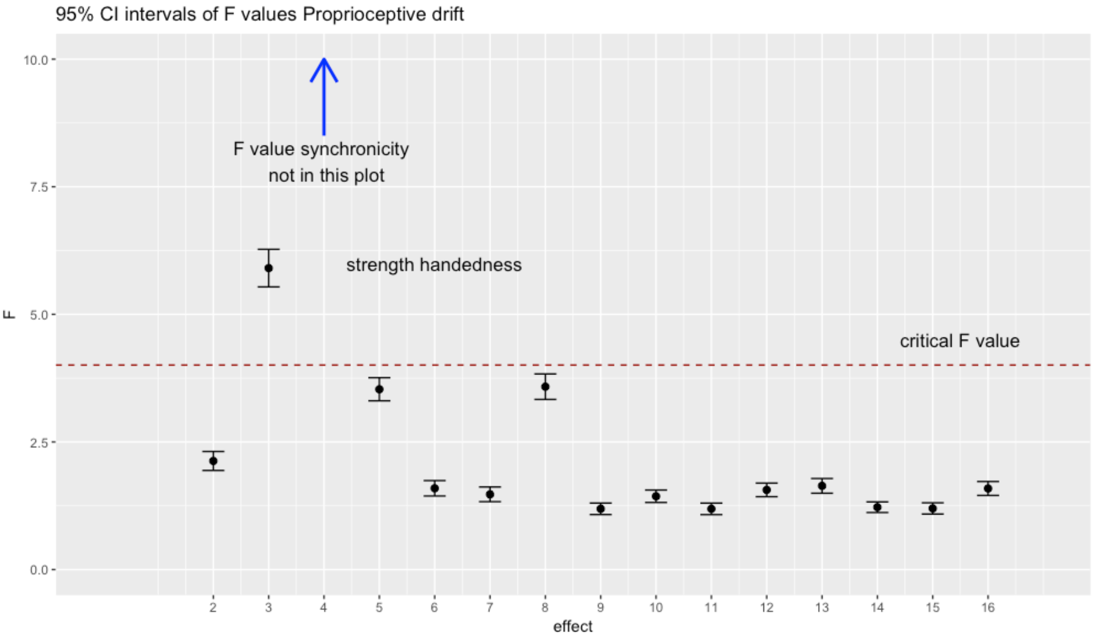

Figure 10. Confidence intervals (95%) of F Values (vertical axis) for each statistical effect (horizontal axis: 2= handedness, 3= strength handedness, 4= synchronicity, 5= hand, 6= handedness x strength handedness, 7= handedness x synchronicity, 8= strength handedness x synchronicity, 9= handedness x hand, 10= strength handedness x hand, 11= synchronicity x hand, 12= handedness x strength handedness x synchronicity, 13= handedness x strength handedness x hand, 14= handedness x synchronicity x hand, 15= strength handedness x synchronicity x hand, 16= handedness x strength handedness x synchronicity x hand). Red dashed lines represents criterion (≈ 4.01).

DISCUSSION

In previous studies, body ownership has been demonstrated to be mainly linked to the right hemisphere and greater interhemispheric connectivity has been shown to be associated with greater right hemispheric activation. Mixed handed participants tend to have more interhemispheric connectivity compared to extreme handed participants (Christman et al., 2008; Prichard et al., 2013). The aim of this study was to examine whether individuals with different handedness preferences differentially experienced feelings of ownership as measured with the RHI. In addition, we examined whether the RHI differed for the left and right hand stroking conditions. Handedness was differentiated in both extreme handed, mixed handed and left-and right-handed individuals. Based on differences in interhemispheric connectivity, we hypothesized a stronger experience of the RHI for mixed handed individuals as opposed to extreme handed individuals. In addition, we expected a higher degree of ownership for the left hand than for the right hand in all handedness groups.

Both subjective (embodiment questionnaire) and objective (proprioceptive drift) outcomes showed that participants experienced the illusion in the synchronous stroking conditions but not the asynchronous stroking conditions, indicating that the RHI was successfully induced. The embodiment questionnaires as well as the proprioceptive drift outcomes indicated that experience of the RHI was similar for sinistrals, mixed handed participants and dextrals. Experience of the RHI was also similar in the left and right hand stroking conditions. Bootstrapping the data for both outcome measures confirmed that after random sampling the data multiple times, there is a high level of confidence that the illusion had no differential impact in either the left or right hand and both handedness groups.

Although previous research showed differences in interhemispheric connectivity (Christman et al., 2008; Prichard et al., 2013; Gutwinski et al., 2011), current results suggests that this affects neither the objective nor the subjective experience of a perceptual illusion of visuotactile integration. This may suggest that ownership may not be as lateralized as current literature indicates. However, since corpus callosum size and subsequent interhemispheric connectivity were not measured directly in the current study, the present results are based on a behavioural measure of laterality only and therefore should not be interpreted without caution. Nevertheless, our findings are consistent with Bertamini and O'sullivan (2014) who suggested that feelings of ownership do not depend on right hemispheric activation only. They state that these feelings of ownership depend more on inter-hemispheric crosstalk, hence the activation of both hemispheres during the illusion. Indeed, Ehrsson et al. (2004) previously provided evidence of bilateral premotor activation (as measured with fMRI), which correlated with the subjective experience of the RHI. Additionally, Kammers et al. (2009) demonstrated that rTMS over the *left* inferior posterior lobule attenuated the strength of the illusion in perceptual body judgments (e.g., proprioceptive judgments). Interestingly, other measures, such as subjective self-reports, were unaffected. However, another study did find differences depending on the hand for which the illusion was induced (Ocklenburg et al., 2011). The reason why Ocklenburg et al., 2011 found a differential effect on handedness might be due to the usage of a different objective measure (i.e., SCR) under threatening circumstances. A high SCR while watching a syringe approaching the hand reflects an autonomic nervous system arousal response, implying an attentional process. Since the right hemisphere is dominant for attention (Heilman & van den Abell, 1980; Kinsbourne, 1970), attentional asymmetries could account for this differential impact. Moreover, recent work (Riemer et al 2015) have shown physiological changes (i.e., SCR) but not proprioceptive changes in the RHI under threatening circumstances, indicating that measures such as drift and SCR might capture different aspects of RHI, especially in an alarming environment.

One alternative explanation for the current lack of differences in RHI strength between the different handedness groups is that our design was not sensitive enough to detect behavioral changes, i.e., we induced the illusion for a fixed time interval (90 seconds). We assumed that the strength of ownership would differentially increase, i.e., higher subjective experience and larger proprioceptive drift. However, since we only measured after the 90 seconds interval, a plateau level of ownership might have been reached, which could have masked subtle differences. In this sense, the exact time to experience the illusion might be more sensitive to detect changes. This is in line with results reported by Niebauer and colleagues (2002). Here participants had to say "now" as soon as ownership was experienced, and this did result in a differential outcome; time to experience ownership increased when laterality quotients increased (Niebauer et al., 2002). Using this manipulation, our results might differ as a function of time instead of strength.

In the present study, we found differences in neither embodiment nor drift between the left and right hand. This is in line with prior research showing no subjective differences for hand being stroked (Mussap & Salton, 2006; Niebauer et al., 2002). Research published while the current research was conducted also failed to show a difference in proprioceptive drift and embodiment questions 1-3 for the left and right hand in a group of dextrals (Bertamini & O'Sullivan, 2014). Interestingly, Bertamini et al. (2011) reported differences in neither proprioceptive drift nor embodiment when visual information was perceived either directly or through a mirror. The RHI thus appears to be undiminished when the left hand is turned into a right hand (Bertamini et al., 2011). Our research is consistent with these results, which is particularly noteworthy concerning literature that linked body ownership to the right hemisphere (Frasinetti et al., 2008; Karnath & Baier, 2010; Tsakiris et al., 2007; Vallar & Ronchi, 2009). Our results suggest that neural representations of ownership over the left and right hand might be similar. In the RHI tactile stimulation is first referenced to a mental body representation and the mental body representation is subsequently updated based on visuotactile integration (Serino & Haggard, 2010; Tsakiris, 2010). Tactile stimulation evokes activity in the contralateral primary somatosensory cortex, the bilateral secondary somatosensory cortex (Ruben et al., 2001), the superior and inferior parietal lobule, the supplementary and cingulate motor area and the insula (Pleger & Villringer, 2013), indicating that the representation of the left and right hand in the somatosensory cortex are similar. Jung, Baumgärtner, Magerl, & Treede (2011), however found a hemispheric asymmetry of hand representation in the somatosensory cortex, i.e., the rostral area was elongated in the left hemisphere as opposed to the right hemisphere due to a larger hand presentation, however this was not statistically linked to handedness. Somatosensory evoked potential studies show differences in neither topography nor response amplitude between the left and right hemisphere (Kakigi & Shibasaki, 1992; Zhu, Disbrow, Zumer, McGonigle, & Nagarajan, 2007). Taken together, this indicates that the reference frame (i.e., mental body representation) and tactile perception of the left and right hand are similar. Although our study complements existing papers on laterality and ownership using similar sample sizes (Niebauer, Aselage, and Schutte, 2002; Ocklenburg, Rüther, Peterburs, Pinnow, and Güntürkün, 2011) we should be careful of making strong claims about a lack of difference, since we are one of the few, if not only, studies that did not find a difference between groups.

In summary, our results show a similar experience of ownership for sinistrals, mixed handed participants and dextrals. In addition, experience of the RHI is similar for the left hand and right hand in all participants. Ownership therefore appears not to be influenced by handedness. In addition, the modifiability in experiencing ownership over a body part is similar for the left and right hand in a healthy population. These results suggest both hands have a similar representation in the brain, which might be useful to keep a coherent sense of the body in space. After resampling our data we can say with high confidence that our outcomes remained unaltered. However different outcome measures, such as skin conductance may reveal other patterns.

ACKNOWLEDGMENTS

We would like to thank Dr. A.M. de Haan for providing support for the bootstrap analyses and Prof. M.J. van der Smagt for improving the overall manuscript.

Chapter 3

Body ownership and the absence of touch: Approaching the rubber hand in- and outside peri-hand space

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Published in: Experimental Brain Research, 2018

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ABSTRACT

It is widely accepted that the integration of visual and tactile information is a necessity to induce ownership over a rubber hand. This idea has recently been challenged by Ferri et al., (2013), as they found that sense of ownership was evident by mere expectation of touch. In our study, we aimed to further investigate this finding, by studying whether the mere potential for touch yields a sense of ownership similar in magnitude to that resulting from actually being touched. We conducted two experiments. In the first experiment our set-up was the classical horizontal set-up (similar to Botvinick and Cohen, 1998). Sixty-three individuals were included and performed the classical conditions (synchronous, asynchronous), an approached but not touched (potential for touch), and a 'visual only' condition. In the second experiment, we controlled for differences between the current set-up and the vertical set-up used by Ferri et al., 2013. Fifteen individuals were included and performed a synchronous and various approaching conditions (i.e., vertical approach, horizontal approach, and a control approach (no hands)). In our first experiment we found that *approaching* the rubber hand neither induced a larger proprioceptive drift nor a stronger subjective sense of ownership than asynchronous stimulation did. Generally, our participants gained most sense of ownership in the synchronous condition, followed by the visual only condition. When using a vertical set-up (second experiment), we confirmed previous suggestions that tactile expectation was able to induce embodiment over a foreign hand, similar in magnitude to actual touch, but *only* when the real and rubber hand were aligned on the vertical axis, thus along the trajectory of the approaching stimulus. These results indicate that our brain uses bottom–up sensory information, as well as top-down predictions for building a representation of our body.

INTRODUCTION

Body ownership is the feeling that your body belongs to you. This feeling of ownership is achieved through integration of visual, tactile and proprioceptive information (Botvinick, 2004; Botvinick & Cohen, 1998; Ehrsson, 2012; Tsakiris, 2017) and can be experimentally manipulated by using the 'rubber hand illusion' (RHI), (Botvinick & Cohen (1998) for a detailed procedure). It is widely accepted that the integration of visual and tactile information is a necessity to induce the rubber hand illusion (Botvinick & Cohen, 1998). However, Ferri, Chiarelli, Merla, Galese, & Constantini (2013) conducted an experiment that challenges this idea. In their study the mere expectation of being touched was used to try to induce a sense of ownership over the rubber hand. Their rationale was that sense of ownership is not only a bottom-up process of sensory input, but also depends on top-down influences. Based on previous experiences, our brain generates predictions about forthcoming events or stimuli (Engel, Fries & Singer, 2001). Ferri and colleagues (2013) hypothesized that the expectation of someone touching the rubber hand is enough to induce ownership over a fake rubber hand. In their set-up the rubber hand was placed above the real hand. The rubber hand and the real hand were not touched in this experiment, but approached slowly from above by the experimenter's hand. Results on the explicit measure (i.e., questionnaire) showed that indeed the mere expectation of being touched enabled a subjective sense of ownership over the rubber hand. Additionally, physiological measures (i.e., skin-conductance responses (SCR)) revealed that this effect was most apparent when the approaching stimulus entered the so called 'peripersonal space' (Ferri et al., 2013) as opposed to extrapersonal space. Thus, Ferri et al., (2013) showed that when a stimulus (i.e., experimenter's hand) enters the peripersonal space (i.e., near hand space), even *expectation* of touch led to ownership over a rubber hand.

This makes sense, since sensory stimuli in peripersonal space are perceived differently than those in extrapersonal space (far space). Research has demonstrated a dynamic and close relation between visual and tactile stimuli in the peripersonal space (Graziano, Hu & Gross, 1997; Rizzolatti, Scandolara, Matelli & Gentilucci, 1981); that is, the multisensory areas in the brain appear to code them in the same way. This was first described in monkeys, where bimodal neurons in the premotor and parietal areas (multisensory areas) respond both to tactile stimuli on the monkey's limb and visual stimuli nearby the limb (Graziano et al., 1997; Rizzolatti et al., 1981). Human behavioural studies yield similar results: Facilitatory effects of tactile processing have been documented when visual attention was directed towards a location close to the tactile target (i.e., vibration on skin) (Driver & Spence, 1998; Macaluso & Maravita, 2010), again this was in near space. Even more so, Kandula, Hofman & Dijkerman (2015) showed that when an arm pointed towards the cheek and was followed by a tactile vibration on that cheek, individuals were faster than when the hand pointed away from the cheek. Cléry et al., (2015[a]) found similar results of enhanced tactile sensitivity with looming stimuli passing the face. These results suggest a visuo-tactile predictive mechanism, where expectation of touch in near space yields faster responses (see review Cléry et al., 2015[b]), and that this integration of spatial and temporal signals may be involved in the same neural networks as multisensory integration is involved (Cléry et al. 2017). Moreover, Dong, Hayashi, Roberts, Fusco & Chudler (1996) reported monkey parietal neurons to respond both when their face was being touched and when a 'harmful' stimulus was held in their peripersonal space (without touching). Therefore, these multisensory brain areas will respond to a visual stimulus that enters one's peripersonal space (without touch) in the same way as when one is actually being touched. That is, these areas also respond to the mere expectation of touch. We know that integration of tactile and visual information has been deemed to be responsible for ownership over a rubber hand. As a consequence, if multisensory areas do respond similarly to mere expectation of touch, then expectation of touch should also induce ownership over a rubber hand. Ferri et al., (2013) confirm this hypothesis. The authors interpreted this finding by suggesting that the sense of ownership was induced by the process of actively produced top-down predictions about forthcoming stimuli, which was based on the idea that sense of ownership is not only a bottom-up process of sensory input, but also depends on top-down influences.

However, although the finding of Ferri and colleagues (2013) is intriguing in itself, the set-up precluded a direct comparison with bottom-up sensory input as it did not make direct comparisons with the conditions that reflect bottom-up processes (e.g., synchronous and asynchronous condition), which are typically used in classical RHI set-ups (e.g., Bovinick & Cohen, 1998). There are some other important differences between the set-up used by Ferri et al., 2013 and classical RHI set-ups. In the study of Ferri et al., 2013 the real hand of the participants was placed *underneath* the rubber hand, instead of next to the rubber hand. Thus when the experimenter approached the rubber hand, the real hand was also being approached. In the current study, by using the horizontal set-up, where only the rubber hand is being approached, we aim to test whether approaching the hands simultaneously is a critical factor in embodying a foreign arm. Furthermore, the experimenter's hand approached the rubber hand slowly *from above* but in lateral view of the participant (i.e., right side), instead of from up front. Related to this, participants in Ferri et al's (2013) study had a *shorter visual exposure* to the rubber hand than in classical RHI studies, as participants were instructed to visually follow the experimenter's hand moving downwards. Inspired by the effect found by

Ferri et al., (2013), we adapted their experiment to match the classical rubber hand set-up (see Botvinick & Cohen (1998) for a detailed procedure; set-up adopted from Kammers, De Vignemont, Verhagen & Dijkerman, 2009), with the only difference being actually touched versus expecting to be touched. Thus, in the current study the rubber hand was placed *next* to the participant's actual hand and we approached the rubber hand from the front, instead of from above. This allowed continuous visual exposure to the rubber hand as well as assessing the sense of ownership over the rubber hand using classical ownership outcome measures (i.e., proprioceptive drift and subjective embodiment). Furthermore, it also enabled us to compare classic multisensory RHI conditions (i.e., synchronous and asynchronous touch condition) to the mere expectation of touch (i.e., hereafter referred to as the predictive condition). We hypothesized that participants would experience ownership over the rubber hand in the synchronous condition as well as in the predictive condition, but not in the asynchronous (control) condition. There is general consensus about the asynchronous condition being a control condition (i.e., no ownership over the rubber hand) (Botvinick & Cohen, 1998; Tsakiris & Haggard, 2005), but see Rohde, Di Luca & Ernst (2011) for a different appraisal of this idea. We also included a visual only condition in which participants merely viewed the rubber hand lying in front of them, without the expectation of being touched or actual touch. Since top down predictions about forthcoming stimuli depend on previous experience (Engel et al., 2001), we further explored whether a previous experience with the RHI modulated sense of ownership in the predictive condition. Half of the participants started with the synchronous stroking condition and the other half with the predictive condition.

METHODS EXPERIMENT 1

Participants

We tested 65 (28 females) neurologically healthy participants. Average age was 43.7 years (Standard Deviation (SD) = 11.6). We recently showed that handedness does not modulate sense of ownership in the RHI (Smit, Kooistra, van der Ham & Dijkerman, 2017), therefore both left and right-handed individuals were included in the current study. Participants were unaware of the purpose of the experiment. They were tested individually and in a laboratory setting inside a museum. It has to be noted that more experimental set-ups were in the same test-room. To minimize distraction, we used large occluders between the set-ups and to keep noise at minimum, we instructed participants to be as quiet as possible. This study was part of Science Live, an innovative research programme of Science Centre NEMO in Amsterdam, where participants were recruited and participated on a voluntary basis for which ethical approval was obtained prior to the study. The study was conducted in accordance with the standards of the declaration of Helsinki and was approved by the local ethical committee. Written informed consent was obtained prior to participation.

Design

The experiment consisted of four conditions in a within subjects design (i.e., synchronous, predictive, asynchronous, visual only, see Figure 1 and 'procedure/task' for details). The experiment was performed in a block-randomized design, in which the experimental conditions were performed first and were then followed by the two control conditions. Half of the participants started with the synchronous condition and the other half with the potential of touch (i.e., predictive) condition. The order of both control conditions alternated as well (see Table 1).

Table 1. *Overview of the experimental design. The conditions were block-randomized, with each participant starting with one of the experimental conditions and ending with both control conditions.*

	experimental conditions		control conditions	
sequence	condition 1	condition 2	condition 3	condition 4
1	synchronous	predictive	visual only	asynchronous
2	synchronous	predictive	asynchronous	visual only
3	predictive	synchronous	visual only	asynchronous
4	predictive	synchronous	asynchronous	visual only

Experimental set-up

The experimental set-up consisted of a wooden box divided in two compartments. The hands of the participants were placed near the sides, with the stimulated left hand being occluded from view (see Figure 1). The rubber hand was placed visibly in the middle part of the box. The distance between the stimulated hand and the rubber hand was approximately 17 cm. The right unstimulated hand also remained visible during the illusion. In addition to a screen that divided the stimulated hand from the rubber hand and the unstimulated hand, a black cloth was placed over the arms of the participants to make the end of the rubber hand and the participant's left arm invisible.

Stimulation

Rubber Hand Illusion: For all participants, all conditions were performed on the left hand for 60 sec. Previous research in our lab deemed 90 seconds of stimulation to be appropriate to successfully differentiate between the synchronous and asynchronous condition. For feasibility reasons we investigated the optimal time window to successfully differentiate between the synchronous and asynchronous condition. Hence, prior to actual testing, we investigated (n=20) whether there were any differences in sense of ownership after 30, 60, 90 seconds of stimulation. Results indicated that the experience of the illusion, as measured with a questionnaire and proprioceptive drift (see appendix 1) did not significantly change as stimulation time increased. Moreover, we found that time-windows of 60 and 90 seconds successfully differentiated between synchronous and asynchronous condition. Thus, for feasibility reasons, we applied a 60 sec stimulation window in Science Live science center NEMO. See appendix 1 for details.

Stroking conditions: There were four conditions (Table 1 for order, and Figure 1 for set-up). In the synchronous condition (Figure 1A), the rubber hand and the real hand of the participant were stroked synchronously in identical stroke frequencies varying from one stroke per second to one stroke per three seconds. In the asynchronous condition (Figure 1B), the rubber hand and real hand were stroked sequentially in an identical pattern wherein the brush only touched one hand at a time. In the predictive condition (Figure 1C) only the rubber hand, and not the real hand, was *approached* from the front and above (red arrow in Figure 1C), but not touched. The approach movement went back and forth (two-sided arrow) once per second and varied in velocity and location in order to reduce habituation effects. In the visual only condition (Figure 1D) participants had to look at the rubber hand.

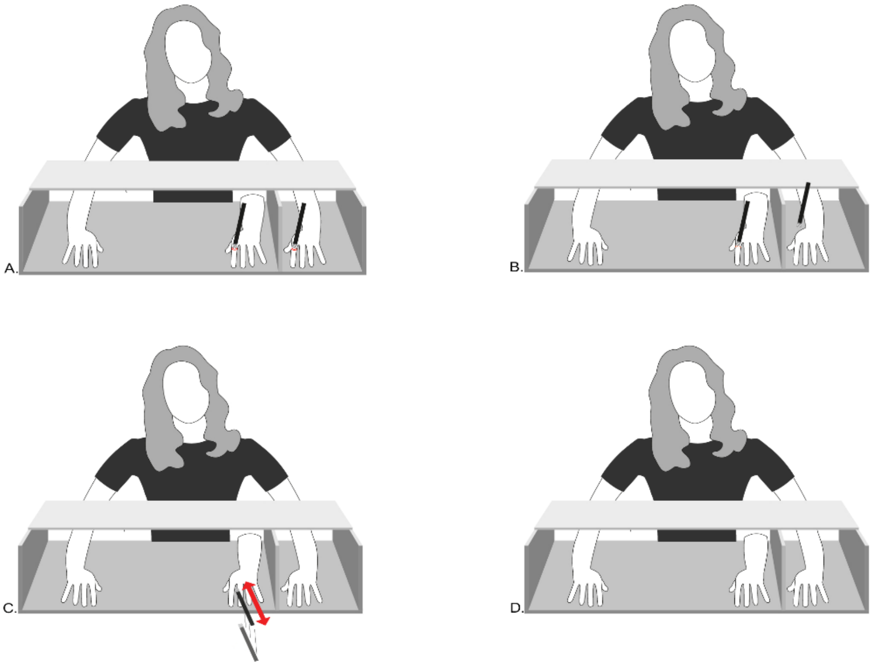

Figure 1. A. Synchronous condition, B. Asynchronous condition, C. Predictive condition, D. Visual only condition. Note that participants did not see their real left hand and that positioning of the hands of the participants was similar in all conditions. To optimize the illusion a black cloth (not shown in Figure) was placed over the shoulder of the participant, which prevented visual feedback of attachment of the own and/or rubber hand to the body.

Procedure and measurements

Prior to the experiment informed consent and demographic information was obtained. First, the hands of the participants were placed in the box and participants were instructed to keep their hands still during the whole experiment (see Figure 1 for positioning). The wooden lid was placed over the box (not shown in Figure 1), which occluded the actual hands and rubber hand from top view. Thereafter the experiment started. The order of measurements was as follows: 1) proprioceptive drift pre-session 2) administration of 60 sec stimulation (i.e., synchronous, predictive, asynchronous or visual) 3) proprioceptive drift post-session after *each* of the aforementioned condition 4) embodiment questionnaire.

Proprioceptive drift. Proprioception or position sense of the left index finger was obtained twice, before and immediately after the stroking. To assess the first measurement of proprioception participants were instructed to close their eyes preventing visual feedback of arm position. A wooden lid was placed on the box, which covered the participant's own hands and rubber hand. The participants were instructed to open their eyes and the experimenter moved his index finger alongside the top of box. Participants had to indicate (by saying stop) when the experimenter’s finger was at the *felt position* of the (left) real index finger. It took approximately 30 seconds between participants closing their eyes, opening their eyes and verbally reporting their estimation. The experimenter measured the felt position, and the real position. A tape-measure that was attached to the back of the set-up allowed for measuring (in centimeters) the felt position and the real position of the center point of the index finger of the participant. The experimenter then removed the top cover of the box for the next trial (either approaching or multisensory stimulation). Participants were instructed to look at the rubber hand, after which one of the four stimulation conditions (i.e., synchronous, predictive, asynchronous and visual) was applied. After stimulation the participants had to close their eyes again, until the top cover was placed on the box. Thereafter participants were instructed to open their eyes again and the post-session of proprioception was obtained. The difference between pre- and post-session is indicative of how much the stimulated hand ‘drifted’ towards the rubber hand. Subsequently, a subscale of an embodiment questionnaire was administered (see below).

*Embodiment questionnaire***.** To indicate the subjective sense of ownership, participants filled out the ‘ownership subscale’ of an embodiment questionnaire (adapted from Longo, Schüür, Kammers, Tsakiris & Haggard, 2008) that contained the following 5 items: 1) It seemed like I was looking directly at my own hand, rather than at the rubber hand; 2) It seemed like the rubber hand began to resemble my own hand; 3) It seemed like the rubber hand belonged to me; 4) It seemed like the rubber hand was my hand; 5) It seemed like the rubber hand was part of my body. The questionnaire was administered on top of the RHI box, preventing visual exposure of the rubber hand. Participants indicated their response with a pencil on a vertical visual analogue scale (VAS) ranging from ‘totally agree’ (top) to ‘totally disagree’ (bottom). A cut-off score was determined based on Longo et al’s (2008) embodiment questionnaire, and was set on the fifth step (+1). If participants scored on average above the cut off score then it is fair to conclude that the illusion was induced successfully.

Analyses

For proprioceptive drift we used baseline corrected difference scores (in cm); we subtracted the felt position before the illusion from the felt position after the illusion. A positive value indicated proprioceptive drift towards the rubber hand, while a negative value indicated that the participant drifted away from the rubber hand. Scores on the Embodiment Questionnaire statements were measured in millimeters (mm) and then converted into percentages. All five statements were averaged. A higher percentage score on the questionnaire represented a higher subjective sense of ownership. Since the assumption of normality was violated for especially the questionnaire measures (discussed below), we used non-parametric tests and presented boxplots (medians) for both outcome measures. We used Related Samples Friedman's Analyses of Variance (hereafter Friedman analyses), and subsequent pairwise comparisons (6) with adjusted p-values (Bonferroni corrected), to test differences between the synchronous, predictive, asynchronous and visual conditions. If not stated otherwise, alpha levels of .05 (two-tailed) were used for the statistical tests. MATLAB was used to generate boxplots. SPSS and JASP were used for statistical analyses.

RESULTS

Ownership questionnaire

For the subjective sense of ownership Shapiro Wilk test for normality revealed that all conditions differed significantly from a normal distribution, all *p-values* $\leq$ .001. Therefore, non-parametric tests were performed. Friedman's Analyses revealed an effect of condition ($\chi2$ (4) = 28.129, $p < .001$. Post-hoc pairwise comparisons for Friedman analyses (Dunn-Bonferroni corrected) showed, as expected, a difference between the synchronous and asynchronous condition ($z = 1.107$, $p < .001$). In fact, post-hoc testing revealed that the synchronous condition differed significantly from *all* the other conditions (asynchronous, predictive and visual), all tests $z \geq .639$, $p \leq .037$ for each comparison (see Figure 2 for individual corrected p-values, left panel). Further testing revealed no difference between the predictive and asynchronous condition ($z = .098$, $p = 1.000$), the predictive and visual condition ($z = -.369$, p = .688) nor the asynchronous and visual condition ($z = -.467$, $p = .274$).

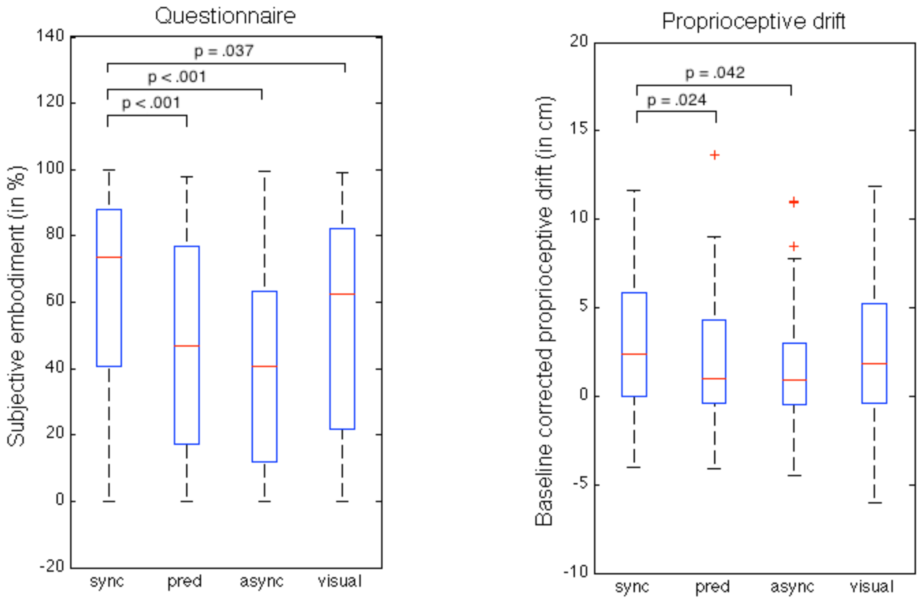

Figure 2. Left panel shows median subjective sense of ownership (in %) and right panel shows the median proprioceptive drift for the synchronous (sync), predictive (pred), asynchronous (async) and visual only (visual) condition. Top lines indicate significant differences between conditions. P-values are Dunn-Bonferroni corrected (6 comparisons per outcome measure). Whiskers represent the data range; minimum and maximum within 1.5 inter quartile range (IQR). The + symbols indicate extreme outliers (>1.5 * IQR). Note that the scales differ because different outcome measures are displayed.

Proprioceptive Drift (PD)

For the proprioceptive drift Shapiro Wilk test for normality revealed that the predictive (*p*= .036) and asynchronous (*p*=.002) conditions differed significantly from a normal distribution. Therefore, for the PD measure non-parametric tests were performed as well. A Related Samples Friedman's Analyses of Variance again revealed an effect of condition, $\chi 2$ (3) = 10.954, *p* = .012. Post hoc pairwise comparisons for Friedman analyses (Dunn-Bonferroni corrected) revealed a significant difference between the synchronous and asynchronous condition *(z* = .631, *p* = .042), and the synchronous and predictive condition (*z* = .672, *p* = .024). Surprisingly, and in contrast to the subjective experience (questionnaire), there was no statistical difference between the synchronous and visual condition (*z* = .303, *p* = 1.000). Also, further testing revealed neither a difference between the predictive and asynchronous condition (*z* = -.041, *p* = 1.000), the asynchronous and visual condition (*z* = -.328, p= .964) nor the predictive and visual condition (*z* = -.369, *p* = .688).

Correlations between the embodiment questionnaire and the proprioceptive drift.

We used Kendall's tau statistic to test whether more explicit accounts of the illusion (the embodiment questionnaire) correlated with the implicit measure of the illusion (position sense of the left index finger). We found a significant positive correlation between the embodiment questionnaire and the proprioceptive drift for the sync condition $\tau_b = .296$, $p < .001$, the pred condition $\tau_b = .412$, $p < .001$, the async condition $\tau_b = .305$, $p < .001$ and the visual condition $\tau_b = .390$, $p < .001$. This relation indicated that, in all conditions, the larger the participants' position sense drifted to right (towards the rubber hand) the higher they rated the subjective experience of the illusion.

Previous experience and the potential for touch

We further explored whether a previous experience of touch in the RHI modulated the sense of ownership in the predictive condition. Half of the participants started with the synchronous stroking condition and the other half with the predictive condition. We found no difference between the predictive condition on position 1 and position 2 (i.e., after the synchronous condition), hence we found no effect of previous multisensory experience on both outcome measures. Likewise, for the synchronous condition order of condition also did not matter, see Table 2 for statistics.

Table 2. *Statistics of both outcome measures (i.e., questionnaire (Q) and proprioceptive drift (PD) for the experimental conditions predictive (pred) and synchronous (sync) on position 1 (P1) or position 2 (P2)*

				95% Confidence interval	
Condition 1	Condition 2	W	*p*	Lower	Upper
predQ P1	predQ P2	246.0	.792	-20.385	25.855
predPD P1	predPD P2	208.5	.629	-2.600	1.950
syncQ P1	syncQ P2	280.0	.542	-10.715	16.865
syncPD P1	syncPD P2	221.0	.604	-2.900	1.650

Note. Wilcoxon signed-rank test.

Control for sequence effects

We block-randomized the conditions (Table 1); the two control conditions (i.e., visual only, asynchronous) were always positioned at the end. As a result, this could cumulatively impact both the outcome measures, that is, the more exposure time the more the illusion is experienced in the visual and the asynchronous conditions. Therefore, additional data (n=28) were gathered where the control conditions were positioned as the first two conditions (n=14 asynchronous on first position visual only on second position, and n=14 vice versa) and compared to the last two positions (position 3 and 4 of the original sample discussed above (*n=33*, *n=30* respectively). Individual Mann–Whitney *U* tests (for between pairs, e.g., position 1 versus 3) and Wilcoxon Rank tests (for within pairs, e.g., position 1 versus 2) were performed to compare the relevant pairs of conditions. No effect of order was found on proprioceptive drift or ownership questionnaire scores for neither the between nor within tested pairs, *all Z-statistics* $\leq$ -.1651, all *p-values* $\geq$ .099.

DISCUSSION EXPERIMENT 1

Results of experiment 1 revealed that *approaching* the rubber hand without touching it did not induce a larger proprioceptive drift or subjective sense of ownership than asynchronous stroking of the rubber hand. Also, a previous experience with the RHI did not modulate sense of ownership in the predictive condition. Generally, our participants gained most sense of ownership in the synchronous condition, followed by the visual only condition. These two conditions did not differ significantly in the (implicit) drift measure.

In the set-up of Ferri et al., 2013, the experimenter's hand was entering the peripersonal space of the real hand since this hand was placed *underneath* the rubber hand and thus in line with the trajectory of the approaching hand. It could be that in our set-up the anatomical (spatial) mismatch between the real and the rubber hand (positioned far apart, with the experimenter's hand only approaching the rubber hand) disrupted the sense of ownership instead of facilitating it. Critically, Ferri & Costantini (2016) wrote a specific commentary on this matter. Here, the authors stated that in order to induce ownership by mere expectation, the approaching movements should be directed towards both hands. It seems that it is this methodological difference (vertical instead of horizontal) that is critical and drives the effect of mere expectation. To directly test this, we performed the experiment again with four different conditions. For the conditions of main interest we used our original set-up in the horizontal plane (i.e., rubber hand lateral to the real hand, (replication of experiment 1) *and* one on the vertical plane (i.e., rubber hand above the real hand). Thus, the latter, vertical set-up was analogous to the set-up of Ferri et al., 2013, except for the fact that we used 60 approaching movements (procedure identical to our experiment 1). In order to investigate the difference between tactile expectancy and actual touch we also used the classical rubber hand set-up (synchronous actual stroking with rubber hand lateral to the real hand). Including this condition allowed us to check whether the participants were susceptible to the illusion (positive control), as it is such a robust and replicable effect (Tsakiris, 2017; Kilteni et al., 2015). We also added a vertical condition where only the rubber hand was approached. The real hand of the participant was on the back, thus testing whether both rubber and own hand need to be in the approach trajectory. Overall, we expected that actual touch induced most ownership over the foreign hand. Because of the spatial alignment of both the real and the rubber hand, we also expect embodiment over a rubber hand in the new vertical set-up, and no embodiment in both the horizontal set-up (replication of experiment 1) and the vertical set-up where the real hand was not present. Like Ferri et al., 2013, we administered the questionnaire of Longo et al., 2008, which consisted of the components 'embodiment', 'loss of own hand', 'movement' and 'affect'.

EXPERIMENT 2

METHODS

Participants

We tested 16 (11 females) neurologically healthy participants. One participant was formally diagnosed with idiopathic sleeping hypersomnia and reported this during testing because of experienced drowsiness and was excluded from the study. Average age of the final inclusion (15) was 22.60 years (SD = 3.22). All individuals were right-handed by self-report. Participants were tested individually and were unaware of the purpose of the experiment. The study was conducted in accordance with the standards of the declaration of Helsinki and was approved by the local ethical committee. Written informed consent was obtained prior to participation.

Design experiment 2

The experiment consisted of four conditions in two different set-ups within subjects design (i.e. synchronous horizontal (syncH), predictive horizontal (predH), predictive vertical (predV) and a predictive vertical control (predVC) condition with no hand in close proximity of the approached rubber hand (i.e. hands were on participants back). Unlike the first experiment, each condition was administered twice in a block-randomized design.

Experimental set-up experiment 2

For the syncH and predH the experimental set-up was identical to experiment 1 except for placement of the right real (unstimulated) hand; in order to keep the vertical and horizontal set-up similar, the right real (unstimulated) hand rested on each participant's lap. The predV set-up consisted of a black box (9 cm in height), with a left rubber hand on top of the box and the participant's real left hand exactly underneath it. The set-up of the predVC was similar to the PredV, only now the real hands were on the participants back, and thus *no* real hands were in close proximity of the approached left-handed rubber hand. Again, as in experiment 1, to optimize the illusion, a black cloth was placed over the shoulder of the participant, which prevented visual feedback of attachment of the own and/or rubber hand to the body.

Stimulation experiment 2

Rubber Hand Illusion: For all participants, all conditions were performed on the left hand for 60 sec (see appendix 1 for data on this).

Stroking conditions: Stroking procedures of conditions syncH and predH were similar to respectively the synchronous and predictive condition of experiment 1. In the predV condition we applied the same approaching movements as in experiment 1, only now the real (unseen) left hand was *underneath* the seen rubber hand (analogous to Ferri et al., 2013). The same approaching procedure was applied in the predVC condition, only now the hands were on the back of the participant. In this case the approaching movement were only directed to a rubber hand. In short, the approach movements in all 'pred'-conditions were identical to the procedure in experiment 1.

*Embodiment questionnaire***.** We administered the questionnaire of Longo et al., 2008, which was the same as Ferri et al., used in 2013. The questionnaire consisted of 10 items for the component 'embodiment', 5 items for the component 'loss of own hand', three items for the component 'movement' and three items for the component 'affect'. Participants had to rate each item on a 7 point likert scale going from *strongly disagree* (-3) to *strongly agree* (3), in which 0 indicates the neutral rating of "neither disagree or agree". Again, the cut-off for experiencing subjective sense of ownership was set on the fifth step (+1). If participants scored on average above the cut off score then it is fair to conclude that the illusion was induced successfully. At the end of the experiment we had an additional question where we asked the participants to rate the overall strength of the illusion (e.g., strength in terms of ownership) for each condition, also on a scale from *very weak* (-3) to *very strong* (3).

Analyses experiment 2

Scores on the Embodiment Questionnaire items were averaged across components. First, we tested whether the observed scores were different from neutral (0). Second, we tested for differences *between* the four conditions. We applied the same procedure for both questionnaires. For questionnaire 1, data approximated normality and therefore parametric tests were used (discussed below). For the second question data violated a normal distribution and therefore we present a table with medians. In the case of parametric data we used a Repeated Measures ANOVA (using Jasp software) and in case of non-parametric data we used Friedman analyses (using Jamovi software). Subsequent pairwise comparisons were Bonferroni corrected. If not stated otherwise, alpha levels of .05 (two-tailed) were used for the statistical tests.

RESULTS EXPERIMENT 2

Embodiment questionnaire

For the subjective sense of ownership Shapiro-Wilk test for normality revealed data approximated normality for all components; only the predVC of the embodiment component (p= .004), and the syncH of the affect component (p=.004) were not normally distributed. All the other 14 'conditions' (4 conditions per component) were normally distributed (range p-value = .067 to p= .916) therefore parametric tests were used. In order to facilitate comparison with results of Ferri et al., 2013 we present means for all the data in Figure 3.

Component Embodiment

All, but predH differed $t(14)$= 1.310, p=.211) significantly from zero for the embodiment component, all tests summarized $t(14) \geq 7.604$, $p \leq .001$. For PredVC this score was negative (Fig. 3), indicating that on average participants did not embody the rubber hand when no hands were present. SyncH and PredV were positive, in these conditions the rubber hand was embodied. Critically, the predH did not differ from zero, indicating, on average, a neutral response for the embodiment of the rubber hand. Repeated measures ANOVA was used to test for differences between conditions, and revealed an effect of condition $F(3,42)$=53.47, p< .001. For post-hoc comparisons, directly testing the two conditions of interest PredV versus PredH reveals us a marginally significant effect $t(14)$=2.583, p= .022, indicating that in terms of expectation of touch we do find more evidence for embodiment in the vertical than in the horizontal set-up. However, we added additional (positive and negative control) conditions (syncH and predVC), and as a consequence this effect did not survive subsequent Bonferroni corrections $t(14)$= -2.583, p= .130 *(pbonf)*. Intriguingly, the syncH did not differ from predV $t(14)$= -1.646, p= .732 *(pbonf)*, indicating both conditions (statistically) did not differ in terms of experienced illusion. SyncH did differ significantly from predH $t(14)$= -4.588, p= .003 *(pbonf)*, and predVC $t(14)$= -10.825, p< .001 *(pbonf)*. As expected, the PredVC differed from all conditions, all tests summarized $t(14) \geq 7.996$, $p \leq .001$ *(pbonf)*.

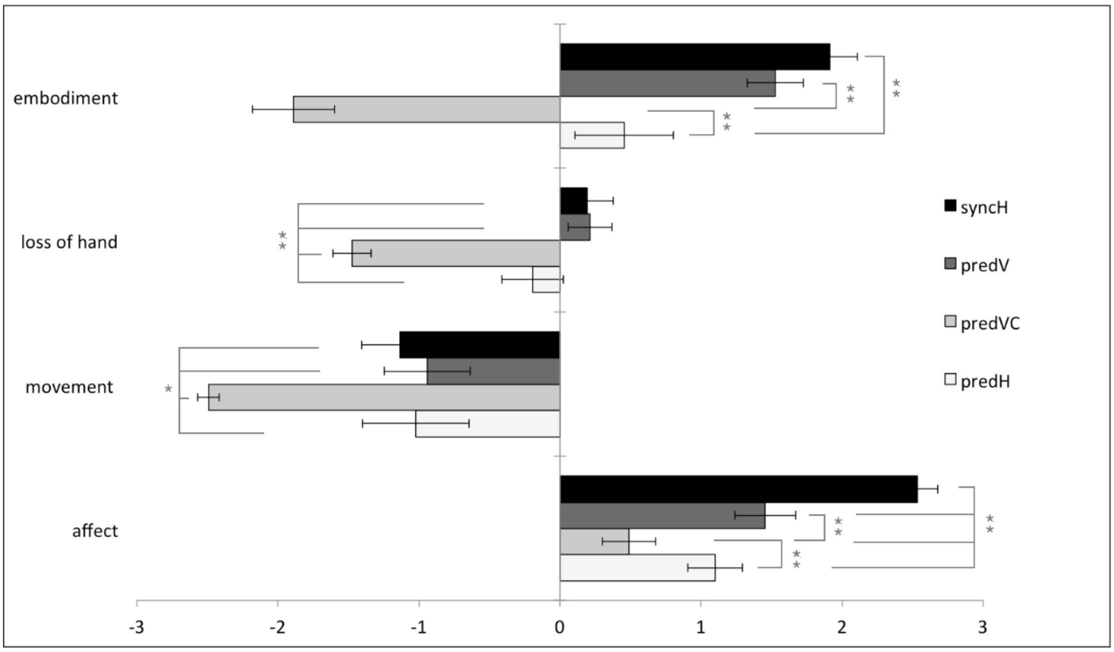

Figure 3. Average subjective ratings of the embodiment questionnaire on the components embodiment, loss of hand, movement and affect for the synchronous horizontal (syncH), predictive vertical (predV), predictive vertical control (predVC) and predictive horizontal (predH) condition. Lateral lines indicate significant differences between conditions (*= $p \leq .028$; ** = $p \leq .002$). P-values are Bonferroni corrected. Error bars represent standard error of the mean.

Component loss of hand

As can be seen in Figure 3, only the predVC control differed from zero $t(14)= -10.968$, $p< .001$, indicating that loss of hand was not experienced in all conditions, all tests summarized $t(14) \geq 1.359$, $p \leq .196$, but especially not in the predVC. We found an effect of condition $F(3,42)=28.32$, $p< .001$, that was mainly driven by the control predVC condition, which differed significantly from all the other conditions, all tests summarized: $t(14) \geq 5.340$, $p \leq .001$ *(pbonf)*. The other conditions did not differ significantly from one another, all tests summarized $t(14)< -2.056$, $p> .353$ *(pbonf)*.

Component movement

On average, the conditions were rated negatively (Figure 3), and one samples-test revealed that all conditions were significantly different from neutral, all tests summarized $t(14) \geq -2.690$, $p \leq .018$. None of the conditions generated the subjective feeling that the hand moved to the rubber hand. Mauchley's test indicated that the movement data violated the assumption of sphericity (p = .018), therefore degrees of freedom were corrected using Greenhouse-Geisser (ε =.738). Repeated measures ANOVA revealed an effect of condition, $F(2.213, 30.985)= 7.714$, $p= .002$, $\eta^2 = .343$. When testing the difference between conditions only the control condition predVC differed significantly between all the other conditions, all tests summarized: $t(14) \geq 3.354$, $p \leq .028$ *(pbonf).* Other conditions did not differ significantly from one another, all tests summarized: $t(14) \leq -.215$, $p = 1.000$ *(pbonf).*

Component affect

All conditions significantly differed significantly from zero, all tests summarized $t(14) \geq -.593$, $= \leq .021$, indicating that the experience was on average enjoyable and interesting, even when no hand was present. Repeated measures ANOVA showed an effect of condition, $F(3,42)=40.53$, $p < .001$. The appeal was especially present for the syncH condition when testing between conditions, since syncH was different from all the other conditions, all tests summarized: $t(14) \geq -6.287$, $p \leq .001$ *(pbonf).* PredH and predV were both different from PredVC, summarized: $t(14) \geq -4.698$, $p = \leq .002$ *(pbonf)*, but not different from each other $t(14) = -2.555$, $p = .137$ *(pbonf)*, indicating that, on average and statistically, participants did not differentiate between these latter conditions in terms of interest and appeal, but did find the experience more pleasant and interesting than in the control condition.

Finally, the cut-off was set at +1, thus according to this criterion participants only experienced the illusion in predV and the syncH, and not in all the other conditions.

Overall illusion strength

At the end of the experiment we asked the participants to rate the overall strength of the illusion (the extent the participant felt the rubber hand was theirs) for each condition, also on a scale from *very weak* (-3) to *very strong* (3).

Data were not normally distributed for any of the conditions $p = \leq .026$, non-parametric tests were used.

One sample Wilcoxon-sign rank test revealed that all conditions differed significantly from neutral (zero), all $W \geq 106.500$, $p = \leq .006$. As displayed in Table 3, participants experienced, on average, ownership in the syncH, predV, and predH, as these conditions were rated positive. Participants reported no ownership in the predVC as this condition was rated negative. Friedman analyses showed an effect of condition $\chi2\ (3) = 37.3$, $p < .001$. Subsequent post hoc comparisons are displayed in Table 3. SyncH now differed from all conditions, and thus was rated most strong. Interestingly, predV differed also from PredH, indicating that the illusion was significantly stronger in the vertical set-up. All conditions differed significantly from the control condition (predVC).

Table 3. *Statistics of the strength of illusion 'questionnaire' for the synchronous horizontal (syncH), predictive vertical (predV), predictive vertical control (predVC) and predictive horizontal (predH) condition.*

Con. 1	*Median*		*Con. 2*	*Median*	*p*	*pbonf*
syncH	**(3)**	**-**	predV	(2)	<. 001	=. 006
syncH	**(3)**	**-**	predH	(1)	<. 001	=. 001
syncH	**(3)**	**-**	predVC	(-2)	< .001	<. 001
predV	**(2)**	**-**	predH	(1)	< .001	=. 006
predV	**(2)**	**-**	predVC	(-2)	< .001	< .001
predH	**(1)**	**-**	predVC	(-2)	< .001	< .001

Note. Wilcoxon signed-rank test.

Verbal reports and observations

Reactions during the syncH condition were unanimously positive and were most often accompanied by a positive affect (i.e., amusement, surprise). Interestingly, the predV evoked more reactions, but these were also more diverse, varying between participants from positive: "This feels more interesting, because my hand is underneath it", "This is so fascinating" to slightly more adverse: "I wanted to withdraw my hand when you approached me", "I wanted to close my eyes every time you almost touched my hand; it was an unsettling feeling" and another participant reported "Every time you approached me, I automatically pressed my own arm against the table surface in order to get sensations in my own hand again". During the predH condition participants seemed less intrigued, and the condition also elicited less reactions, these were similar to reactions in experiment one. Some participants "felt air and wind" on their own hand, a few participants reported the experience of "sensations like pins and needles" on their own hand. One participant reported "I am having three hands, while my head tries to make it one percept, I still perceive it as three where I could not move my own hand". The predVC evoked almost no reaction; the rubber hand felt like an external object "this hand felt very alien to me".

DISCUSSION EXPERIMENT 2

In this experiment we aimed to explore possible factors that had contributed to the discrepancy in the findings of experiment 1 and those of Ferri and colleagues (2013). We compared the vertical set up of Ferri et al., (2013), wherein we integrated our own approaching procedure, with the classical horizontal rubber hand set-up (both synchronous actual stroking with rubber hand and approaching the rubber hand). Lastly, as a control, we also added a condition where only the rubber hand was present. Here, the rubber hand was placed in vertical axis and was approached with a brush, only now no real hand was placed underneath it.

Our results revealed that on average the syncH and predV did not significantly differ from one another in most of the components, except for the affect component where actual touch was experienced as more pleasant. The latter finding was confirmed by verbal reports. We cautiously suggest that expectation or potential for touch and actual touch both elicit the illusion to a similar extent. We, however, have to note that the difference between the vertical approaching movements and the horizontal approaching movements did not survive Bonferroni corrections for the embodiment component, while actual touch consistently differed from the horizontal approaching movements. When isolating the effect of our vertical approach set-up and comparing it directly to Ferri et al's findings, we see a similar pattern of results, albeit the absolute magnitude is slightly smaller than the effect seen in Ferri et al., 2013 (see general discussion). We do agree with their commentary that, in order to embody a fake rubber hand, touch is not a necessary component *if* there is spatial and temporal contiguity; the rubber hand and the real hand have to be along the same trajectory (see general discussion). When, however, the rubber hand and the real hand are spatially aligned, but not in close proximity and not along the same trajectory (as in the horizontal condition), the relationship between the event and the expectation of touch becomes less causal, and embodiment is less likely to occur (see Woods et al., 2014).

GENERAL DISCUSSION

Ferri and colleagues (2013) have shown that a sense of ownership over a foreign body part can occur as a result of the expectation of touch. In our study, we performed two experiments to further investigate whether the mere potential for touch (top-down process) yielded a sense of ownership similar in magnitude to that resulting from the multisensory stimulation (bottom-up process). Inspired by the finding of Ferri and colleagues (2013), in experiment 1, we added an extra condition (i.e., potential for touch) to the classical rubber hand set-up (see Botvinick & Cohen (1998); set-up adopted from Kammers et al. (2009)), so that the only difference between conditions is either actually *being* touched or *expecting* to be touched. Although set-ups are different, conceptually a replication of Ferri et al's (2013) results would mean that expectation of touch could be deemed sufficient to induce a sense of ownership over a foreign body part. Our results in experiment 1 revealed that *approaching* the rubber hand without touching it did not induce a larger proprioceptive drift or subjective sense of ownership than asynchronous stroking of the rubber hand. In general, our participants gained most sense of ownership in the synchronous condition, followed by the visual only condition. These two conditions did not differ significantly in the (objective) drift measure. Interestingly, Rohde et al. (2011) reported a similar result: They also found that visual exposure made the participants' perceived hand location drift to the rubber hand to a similar extent as the synchronous condition did. Rohde et al. (2011) stated further that "proprioceptive drift in the RHI may not be caused by synchronous stroking, but rather that its lack may be caused by asynchronous stroking in the control condition". Their study proposes a dissociation between the proprioceptive drift measure and the questionnaire; the former is caused by visuo-proprioceptive integration, and the latter by multisensory (i.e., visual, proprioceptive and tactile) integration. Thus, for proprioceptive drift, asynchronous stroking disrupts this visuo-proprioceptive integration. Intriguingly, our results show a (positive) relation between the proprioceptive drift and the questionnaire, indicating at least partial overlap between the underlying mechanisms (see Tajima et al., 2015). However, our data also concur with Rohde et al., (2011); for proprioceptive drift to occur visuo-proprioceptive integration is deemed responsible. In our set-up the proprioceptive alignment (i.e., the spatial alignment of the hands in anatomical similar position) plus the visual capture of the rubber hand indeed induced a drift, which was statistically not distinctive from multisensory stimulation (i.e., proprioceptive, tactile and visual information). In other words, actual touch did not add more drift than visual and proprioceptive input alone. However, proprioceptive drift in the visual condition was different compared to the asynchronous condition, hence, asynchronicity disrupted potential drift. Thus we confirm findings of Rohde et al., (2011): For the proprioceptive drift measure visuo-proprioceptive integration seemed to cause the drift, and asynchronicity disrupted it. In contrast, for the embodiment questionnaire, multisensory stimulation (i.e., proprioceptive, tactile and visual information) differed from all the other conditions, indicating that the effect in more explicit accounts of the illusion was actually driven by multisensory integration. Thus as Rohde et al., 2011 suggested, for both measures different underlying mechanisms seem responsible.

One could further argue that in our set-up the 'predictive' condition accounting for the potential of touch, with its approaching movements, disrupted the illusion to a similar extent as the asynchronous condition did. If we take a closer look at what the predictive condition entails, we observe the same kind of phenomenon as in the asynchronous condition; in the asynchronous condition participants expected to feel the touch that they see, but did not feel it simultaneously. The *temporal* disparity between the seen and felt touch 'disrupted' the illusion. In the predictive condition participants expected to be touched, but the touch never comes, which violates the expectation of touch. Anecdotal reports during experiment one confirmed this; touch was expected, but never occurred, which could have disrupted embodiment. However, expectation of touch did occur in the set-up of Ferri et al., 2013. The difference in set-up seems crucial; the experimenter's hand was entering the peripersonal (hand) space of the real hand, since this hand was placed *underneath* the foreign hand and thus in line with the trajectory of the approaching hand. In other words, in this case it is the *spatial* disparity that seems critical; in our set-up the spatial mismatch between the real and the rubber hand (positioned further apart, with the experimenter's hand only approaching the rubber hand) disrupted the sense of ownership instead of facilitating it.

Ferri and Costantini (2016) wrote an insightful commentary on this specific matter. They stated that, in order to experience embodiment over a rubber hand, tactile expectation should be generated on both the rubber hand and the real hand, in the same path or trajectory. When the own hand is outside this path, the illusion will be less vivid. The fact that tactile expectation can evoke embodiment over a foreign arm is already intriguing, but why does it differentiate between a vertical or horizontal position, more specifically why does expectation of touch only elicit a vivid illusion when the hand is within the peri-hand space and not when it is lateral to the rubber hand, but still very close? According to the Bayesian statistical inference framework, prior life experiences in sensory regularities (e.g., spatial and temporal consistency) allow us to make inferences or predictions about forthcoming events (Friston et al., 2016; Friston et al., 2010). Our brain shapes these predictions by updating the prediction to the actual outcome (i.e., Bayesian updating). If we apply this framework to our manipulations, in our experiments we attempted to induce a *visuo-tactile* inference, that is, a visual event, such as an approaching object towards the hand, is likely to predict (based on prior or innate experiences) a tactile consequence (i.e., it will cause a touch on the hand). Causality between the visual and tactile event is more likely to occur when temporal events (e.g., when do I feel the touch) and spatial characteristics (e.g., is that going to touch me) follow the same rules that we learned in prior experiences. Thus, touch is more likely to occur or to be predicted when the rubber and real hands are spatially aligned with the trajectory of the approaching stimulus, than when they are not positioned along the same trajectory. We tested this in our second experiment and confirm that tactile expectation was able to induce embodiment over a foreign hand, to a similar extent as actual touch did, but *only* when the real hand was aligned with the path of the approaching stimulus. When the hand was slightly further away, i.e., lateral to the real hand, responses were not different from neutral. We also observed that approaching only a rubber hand while the real hands were anatomically misaligned to the rubber hand (i.e., on the participants back), which violated the spatial consistency, no embodiment occurred (different from neutral). We suggest that a complex interaction between the bottom-up properties of bimodal neurons (i.e., cells that respond both to visual and tactile information near the body) and higher order visuo-tactile inferences are involved in building a representation of our body.

In a recent study, Ferri and colleagues replicated their own findings in 2017 for the questionnaire, which was their sole outcome measure for the vividness of the illusion as well. They also recorded neural activity using near-infrared spectroscopy (fNIRS). Here they found more activation in the multisensory areas, i.e., the inferior parietal cortex, contralateral to the 'approached' hand than when a wooden hand-like object was approached. Again, this shows that our brain does not only 'wait' for incoming (bottom-up) sensory stimuli to form a representation of the body, but it also generates active top-down predictions about the bodily consequences of surrounding sensory events to the extent that these predictions can change the representation of our body. To go one step further, a recent study (Kilteni & Ehrsson, 2017) found that illusions in body ownership also influenced sensory prediction. Here, the authors found that experiencing hand ownership produced somatosensory attenuation during self-touch. Thus, sensory prediction does not only influence the representation of the body (as in our case), bodily illusions also influence sensory expectations (for further reading see Kilteni & Ehrsson, 2017). With respect to differences in actual touch and predictive touch, future studies should test how strong the predictive effect is compared to actual touch; does actual touch (compared to predicted touch), follow the same pattern of activation in the multisensory areas. As a sidenote, we found in our data that the affect component, which comprises of enjoyment, appeal and pleasantness, actual touch did differ from all the other conditions. Thus, although the rubber hand could be embodied similarly between mere expectation and actual touch, the affective component was less vivid for mere expectation. In fact, some participants found the approach movement quite unsettling, and felt like retracting their own real hand.

Thus overall, we directly tested Ferri and Costantini's (2016) suggestion that the space or trajectory wherein these approach movements occur is critical for the illusion to be experienced. In two experiments we compared a set-up in which a vertically aligned rubber hand and one's real hand were approached in the same approach movement, with a more classic set-up in which the rubber and real hand were positioned in lateral fashion and where the rubber hand was approached only. We confirmed that only when both hands are along the same approaching trajectory, the mere expectation of touch was able to induce ownership over the rubber hand. Overall, these findings confirm the original observations by Ferri et al. (2013) and the suggestion made by Ferri and Costantini (2016). When isolating the embodiment component of our vertical set-up and compare it directly to the observed effects their study of 2013, we still see a similar pattern of results, albeit the absolute magnitude of this component is slightly smaller than the effect seen in Ferri et al., 2013. However, in their most recent study, the effects on the embodiment component were also more reduced (Ferri et al., 2017). Apart from the aforementioned set-up (horizontal versus vertical) differences, we have to note other methodological differences that could account for differences. Firstly, in our task we approached the rubber hand approximately sixty times, whereas Ferri et al., 2013 approached the hand only four times. We concluded from earlier pilot-sessions that if we varied the velocity and the potential location of touch then habituation was less likely to occur. However, the likelihood of becoming habituated is still higher when the hand is approached sixty times instead of four times. Second, although, we block randomized our design; the addition of an actual touch condition might have attenuated the effect in the predictive condition. Although, one might argue that actual touch might facilitate mere expectation, we did not find this in our first experiment. Moreover, Ferri et al., (2013) found an effect for near space using SCR. In their set up, participants had to look at the (experimenter's) hand approaching (from above) and not at the rubber hand in front of them, the latter being constantly looked at in the classical set-up (Botvinick & Cohen, 1998). In this regard, when the approaching hand is far up, participants do not see the rubber hand in front of them. It is therefore intuitive that no ownership is present for the simple reason that the rubber hand is not in sight. When the experimenter hand (from above) moves closer to the rubber hand, the participant gradually sees something laying in front of him that resembles a real hand, but this is still in the visual periphery. Incorporating something that roughly looks like a hand to our own body scheme is more likely in this sense (Tsakiris, 2017). The question remains whether peripheral vision introduced an error and the participant mistook the fake embodied hand for his or her own. It would be interesting to test whether this effect for near space could be replicated if the hands were approached from up front, in this case, visual input is kept constant. Finally, while SCR was used in their study, we used proprioceptive drift as an objective outcome measure, the latter being a somewhat direct measure of body ownership. SCR is also an interesting bodily measure, since it reflects bodily arousal, but has also been associated with emotional and affective states (Rohde et al., 2011), and might thus also reflect other processes, rather than body ownership per se. In order to have a behavioural, implicit measure (as opposed to the questionnaire) of the vividness of the approach movements, it would be interesting to test whether the position sense of the real hand drifted in the vertical axis, i.e., towards the rubber hand, after mere expectation of touch.

All in all, in our first experiment we found that *approaching* the rubber hand neither induced a larger proprioceptive drift nor subjective sense of ownership than asynchronous stimulation did. Generally, our participants gained most sense of ownership in the classic synchronous condition, followed by the visual only condition. When directly comparing the horizontal set-up of experiment 1 with the vertical set-up of Ferri et al., (2013) in experiment 2, we found that tactile expectation was able to induce embodiment over a foreign hand, similar in magnitude as actual touch, but *only* when the own hand was placed along the path of the approaching stimulus. This is in accordance with previous results (Ferri et al., 2013; Ferri et al., 2017) and suggestions (Ferri and Costantini, 2016). These results suggests that our brain uses bottom–up multisensory information, as well as top-down predictions about anticipated sensory input to represent our body or induce changes in the representation of our body.

APPENDIX I

Aim and design pilot experiment

This study was part of Science Live, an innovative research programme of Science Centre NEMO, where participants were recruited. As such we had to limit the time per participant. Therefore, we ran a pilot study prior to the experiment in Science Live in our own lab. Here we were mainly interested in whether stimulation time could differentially impact proprioceptive drift and an embodiment questionnaire, our primary outcome measures. If so, we would choose the stimulation time that was both feasible in the Science Live test setting and that also differentiated between the classic synchronous and asynchronous condition. Therefore, we used the classical condition (i.e., synchronous versus asynchronous) and three stimulation times (i.e., 30 sec., 60 sec., 90 sec.) and measured both proprioceptive drift and the five statements mentioned in the manuscript. Conditions were randomized for each participant.

Demographics

Twenty students participated in this pilot experiment. There were five males and fifteen females, with a varying age from 20 to 25 years (M=21.85; SD=1.42). Informed consent was obtained prior to the experiment.

Analyses

For proprioceptive drift we used baseline corrected difference scores (in cm), see result section in manuscript for exact calculations. Also, we used the same five Embodiment statements with the only difference that we used a 10 point-scale (agree vs. disagree), in which a cut-off score for experiencing a subjective sense of ownership was set at 5. Normality was violated especially for the questionnaire measures, and thus we used non-parametric tests and present boxplots (medians) for both outcome measures. We used Related Samples Friedman's Analyses of Variance (hereafter Friedman), and subsequent post-hoc tests between synchronous and asynchronous conditions using Wilcoxon Ranks test with adjusted p-values (Bonferroni corrected). If not stated otherwise, alpha levels of .05 (two-tailed) were used for the statistical tests.

Ownership questionnaire

For the subjective sense of ownership Shapiro Wilk test for normality revealed that all but one condition (synchronous stroking for 60 seconds; $w = .921$, $p = .012$.) approached a normal distribution, all other conditions summarized: $w > .927$, $p > .104$.

As expected, Friedman's analysis revealed an effect of synchronicity ($\chi2$ (2) = 44.085, $p < .001$, but no effect of stimulation time ($\chi2$ (2) = 4.560, $p = .104$ on the ownership questionnaire. Friedman's analyses does not allow interactions between synchronicity and stimulation time, therefore we subtracted the asynchronous score from the synchronous score and analyzed whether this 'true' illusion score changed as a function of stimulated time; Friedman analyses revealed that the illusion score did not significantly change as stimulation time increased (χ2 (2) = 1.658, p = .451.

Furthermore, post hoc pairwise comparisons showed a difference between the synchronous and asynchronous condition after 30 seconds stimulation time (Z = -3.138, p = .002, *pbonf= .006*), 60 seconds stimulation time (Z = -3.827, p < .001, *pbonf= .003*), and 90 seconds stimulation time (Z = -3.885, p < .001, *pbonf= .003*), see Figure 1 appendix, left panel.

Proprioceptive drift

For the proprioceptive outcome measure Shapiro Wilk test for normality revealed that synchronous stroking of 90 seconds and both the asynchronous stroking of 30 and 60 seconds were not normally distributed, all tests summarized: $w \leq$ .926, $p \leq$ .013. Other conditions approached a normal distribution, all conditions summarized: $w \geq$ .927, $p \geq$ .104. As expected, Friedman's analyses revealed an effect of synchronicity (χ2 (2) = 11.655, p = .001, but no effect of stimulation time (χ2 (2) = 4.179, p =125. Therefore we subtracted the asynchronous score from the synchronous score and analyzed whether this 'true' illusion score changed as a function of stimulated time; Friedman analyses revealed that the illusion score did not significantly change as stimulation time increased (χ2 (2) = .300, p = .910. Furthermore, post hoc pairwise comparisons showed a difference between the synchronous and asynchronous condition for 30 seconds stimulation time (Z = -2.054, p = .040, *pbonf = .12*), 60 seconds stimulation time (Z = -2.677, p = .007, *pbonf= .021*), and 90 seconds stimulation time (Z = -2.496, p < .013, *pbonf*= .039), see Figure 1 appendix, right panel.

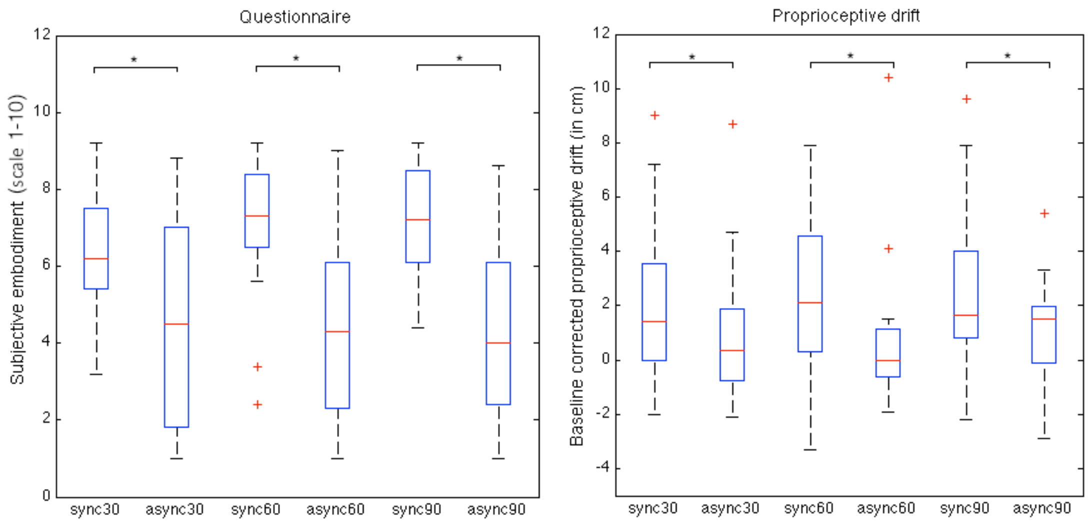

Figure 1 appendix. Left panel shows median subjective sense of ownership (ownership subscale only) and right panel shows the median proprioceptive drift for the synchronous (sync), and asynchronous (async) condition for all time intervals (30, 60, 90 seconds). Top lines indicate significant differences between conditions. Whiskers represent the data range; minimum and maximum within 1.5 inter quartile range (IQR). The + symbols indicate extreme outliers (>1.5 * IQR). Note that the scales differ because different outcome measures are displayed.

CONCLUSION

From this pilot study we can safely conclude that the experience of the illusion, as measured both subjectively and objectively did not significantly change as stimulation time increased. Moreover, we found that time-windows of 60 and 90 seconds successfully differentiated between synchronous and asynchronous condition. For the 30-second window this was the case for the questionnaire only, proprioceptive drift did not survive subsequent bonferroni corrections. In Science Live science center NEMO we therefore used 60 seconds of stimulation time.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ACKNOWLEDGMENTS

We would like to thank S. Smit for designing the experimental set up (Figure 1).

Chapter 4

Changes in perceived peripersonal space following the rubber hand illusion

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Published in: Scientific Reports, 2023

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ABSTRACT

Peripersonal space (PPS), the region immediately surrounding the body is essential for bodily protection and goal directed action. Previous studies have suggested that the PPS is anchored to one's own body and in the current study we investigated whether the PPS could be modulated by changes in perceived body ownership. While theoretically important, this anchoring can also have implications for patients with altered body perception. The rubber hand illusion (RHI) is a way to manipulate body ownership. We hypothesized that after induction of a left hand RHI, the perceived space around the body shifts to the right. Sixty-five participants performed a landmark task *before* and *after* a left hand RHI. In the landmark task, participants had to determine whether a vertical landmark line was left or right from the center of a horizontal screen. One group of the participants was exposed to synchronous stroking, the other group experienced asynchronous stroking. Results showed a shift in space to the right (e.g., away from the own arm), but only for the 'synchronous stroking' group. These results suggest that the relevant action space becomes linked to the fake hand. Critically, subjective ownership experience did not correlate with this shift, but proprioceptive drift did. This suggests that multisensory integration of bodily information drives this shift in space around the body and not feelings of ownership.

INTRODUCTION

Multiple senses give us feedback that our body belongs to us (Azañón et al., 2016). We can continuously see our body, we can feel touch through mechanoreceptors on our body, and we get feedback about the joint angle, muscle tension and muscle length regarding the location of our limbs. The integration of these senses, i.e., vision, touch and proprioception, contributes to creating awareness of our body and gives us the feeling that our body belongs to us, which is commonly referred to as body ownership (Gallagher, 2000). Body ownership (BO), or more specifically arm ownership, can be experimentally manipulated; a well-known way to do so is the Rubber Hand Illusion (RHI) (Botvinick & Cohen, 1998). In the classic RHI a rubber hand is placed next to a subject's own hand. Both hands (i.e., real and rubber) are stroked in synchrony at the same location, with only the rubber hand being visible. Watching the rubber hand being stroked, while simultaneously feeling the strokes on one's own hand, causes the rubber hand to be attributed to one's own body (Tsakiris & Haggard, 2005). In order to integrate the new hand into the body representation, it is important that both the rubber hand and real hand are anatomically aligned (Makin et al., 2008; Pavani et al., 2000; Tsakiris & Haggard, 2005). In other words, they should be positioned in the same orientation and in parallel (Botvinick & Cohen, 1998) - to each other or above one another (Ferri et al., 2013). Embodying the rubber hand as your own changes the sense of location of your own hand, that is, the perceived location of one's own hand typically 'drifts' towards the rubber hand after inducing the illusion. This phenomenon is known as 'proprioceptive drift' (Botvinick & Cohen, 1998). The RHI illustrates the plasticity of our body representation; it transiently changes how and where we perceive our hand.

Several studies suggest that perception of space and body ownership are linked. Ocklenburg et al. (2012) investigated the influence of body ownership on pseudoneglect (i.e., a slight asymmetry of spatial attention *to the left* in healthy individuals) using a line bisection task (Thomas & Elias, 2010). Results indicated a reduction of pseudoneglect, but only after left hand RHI in high responders (i.e., participants who had a vivid rubber hand illusion). Interestingly, this reduction was not found in low responders (i.e., participants who showed a less strong illusion). These findings concur with a case displaying visuospatial neglect (Kitadono & Humphreys, 2007). After the induction of a right hand RHI this patient showed a transient improvement of neglect on a cancellation task and line bisection; presumably the subjective midline shifted to the left allowing more space on the left side to be explored. Ocklenburg et al. (2012) proposed that the subjective midline shifts to the right after the left hand RHI (as the left rubber hand is closer to the body midline than the real left hand), and therefore stimuli in space also shift to the right (i.e., the score on a line bisection task). However, in their study they did not directly test the perceived direction of the body's sagittal axis, i.e., the subjective midline. Moreover, the line bisection task involves a motor response (i.e., actively bisecting the line). Another task that is often used to determine space perception asymmetries is the landmark task (Milner et al., 1993). In this task, a horizontal line is pre-bisected by a short vertical line, the landmark. The participant is asked to indicate whether the landmark is closer to the left or the right end of the horizontal line. Neglect patients generally indicate the left end of the line to be closer when the landmark is equidistant from both ends, suggesting that a lack of attention results in an underestimation of the perceived left half of the line (Harvey et al., 1994; Milner et al., 1993). Similarly, healthy participants show a slight overestimation of the extent of the left part of the line, consistent with pseudoneglect, on the landmark task (Heber et al., 2010; Milner et al., 1992). The landmark task, in principle, is a visuospatial perceptual task, which can be performed without reference to the body. However, experimental studies have shown that the bias in landmark performance, depends on the distance of the lines from the body. When located in extrapersonal space, the leftward landmark bias is reduced or even absent (Heber et al., 2010; Longo et al., 2015; McCourt & Garlinghouse, 2000). This suggests that performance on the landmark task near the participant involves mechanisms that differ from those used further away (Longo & Lourenco, 2006). One important difference may be that near the body, the judgement of the location of the landmark also involves using a bodily reference frame.

In the current study we therefore examine whether altering the body representation using the rubber hand illusion influences performance on a purely perceptual spatial task, the landmark task. Specifically, our aim is to investigate whether a change in hand ownership caused by a left hand rubber hand illusion influences the landmark bias. The landmark task, which requires the participant to indicate whether a transection mark was located to the left or right of the center of a horizontal monitor was used *before* and *after* the RHI. Ocklenburg et al. (2012) suggested that a shift in the subjective midline towards the right, as a consequence of feeling ownership over a left rubber hand, influenced the line bisection. We therefore also measured the subjective midline by a subjective straight ahead pointing task *before* and *after* the RHI. This task required participants to point straight ahead, while blindfolded, to where they thought their bodily midline was. A between subject design was used with one group receiving synchronous stroking in the RHI set-up (presumed to induce the RHI), and a second group receiving asynchronous stroking (presumed to *not* induce the RHI). We anticipated that, because the rubber hand is located closer to the body midline (i.e., more to the right), inducing a left RHI in the synchronous group, would result in a rightward shift in body midline and hence a rightward shift in spatial perception as measured with the landmark task. We did not expect such a shift in the group which received asynchronous stroking.

METHODS

Participants

In total, 65 undergraduate and graduate students participated in this study. The Embodiment Questionnaire (Kammers et al., 2009) was used to define to what extent participants experienced the illusion in both the synchronous stroking group (SG) and the asynchronous stroking group (AG). The synchronous group only received synchronous visuo-tactile stimulation when exposed to the rubber hand. In contrast, the asynchronous group only received asynchronous visuo-tactile stimulation.

All participants were right-handed by self-report. Participants received course credits or 6 euros as a compensation for their time. They were naïve to the purpose of the study and a written informed consent was obtained from all individual participants prior to the experiment. This study was conducted in accordance with the standards of the declaration of Helsinki and was approved by the FETC of the Faculty of Social and Behavioural Sciences at Utrecht University.

Table 1. *Participant demographics for both the Synchronous Group, and Asynchronous Group (see text for details).*

	N	Age (SD)	Gender F/M
Synchronous Group	29	21.83 (2.00)	26/3
Asynchronous Group	36	23.44 (5.15)	28/8

Design

We conducted a pre-post between subjects design with type of stroking (i.e., either synchronously or asynchronously) as the between subjects factor. All participants completed several pre- and post-illusion measures (see task/stimuli below for detailed information for all the measures) in the exact same order (Figure 1). Our primary outcome measure was an estimate of the point of subjective equality (PSE, see Analyses for details) generated from the pre- and post-Landmark tests. The test procedure started with the pre-measure of straight ahead pointing (SAP) followed by the pre-measure of the proprioceptive drift and the pre-session of the landmark-task (LM). Thereafter the RHI was induced (i.e., either synchronously or asynchronously depending on the group); the post-session of the proprioceptive drift, the landmark and straight ahead pointing followed the illusion respectively. In order to check whether the illusion was well executed, the proprioceptive drift (e.g., behavioral measure) measure followed the RHI immediately instead of the post-test of the Landmark. Ultimately, the embodiment questionnaire was administered.

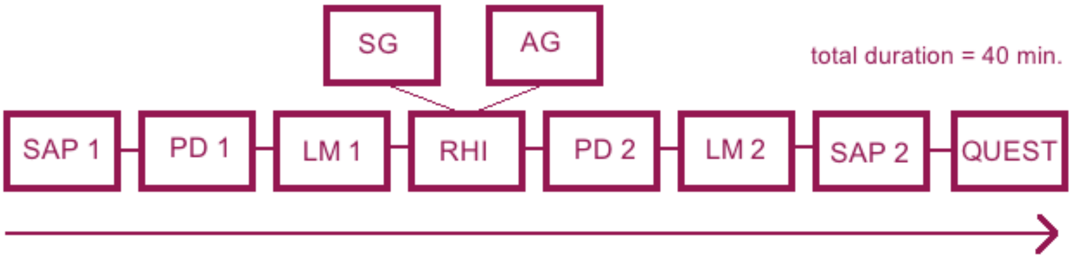


Figure 1. Timeline of the design: From left to right: SAP= straight ahead pointing, PD= proprioceptive drift, LM= Landmark, RHI= Rubber Hand Illusion, SG= synchronous stroking group, AG= asynchronous stroking group, 1 indicates the pre-measure, 2 indicated the post-measure. See Task/Stimuli for details of the tasks.

Stimuli/Procedure

Prior to the experiment participants were asked to remove all jewelry (i.e., rings and watches). The participant then seated oneself at the long end of a table, in front of a large horizontal screen (55inch) (see Figure 2). The participant’s head was stabilized with a chinrest. For an overview of the set-up, see Figure 2.

Straight ahead pointing

The first experimental task was the straight ahead pointing (hereafter SAP, reflecting the subjective body midline), the participants placed their lower arms on the screen, in front of their body (wrists at 32.5 and 102.5 cm from the left side of the tablet). The participants were instructed to point, with eyes closed to prevent feedback, with either their left or right hand at their own body midline and then in front of them where this midline would be on the monitor. This procedure was then repeated for the other hand. These locations were measured in cm from the left side of the tablet with a tape measure. For analyses, the SAP’s (in cm) were only used from the right hand as the left hand could have been influenced by the RHI, and the pre- and post-measures (cm) were included in the analysis. The duration of this task was about 3-5 minutes.

Proprioceptive drift

After the SAP the *pre-measure* of the proprioceptive drift was conducted. A black occluder was placed over both hands to make them invisible, see Figure 2b. The experimenter moved a stick from left to right (or right to left, random sequence) alongside the long end of the table. Participants were instructed to say stop when the stick was at the *felt* location of left or right index fingertip (again random sequence). The experimenter documented the exact location (by means of a tape measure) of the reported felt position. The left finger was always located 32.5 cm from the left edge of the box. The right index was 102.5 cm from the left edge of the box, see Figure 2a. Thereafter, the occluder was removed. The pre- and post-measure (cm) were included in the analysis. The duration of this task was about 3-5 minutes.

Landmark task

After the administration of the pre-test for proprioception, the pre-landmark task started. Participants were instructed to determine whether a landmark (i.e., vertical transection mark) was either left or right from the center of a grey line (Figure 2c). In order to prevent feedback from previous landmark positions, each trial started with a static dot (500 ms) (Figure 2c) appearing either on the left and right (alternately) from the center of the screen. Participants were instructed to look at these dots. Then a horizontal (dark grey) line across the whole width of the monitor (light grey background) was presented (Figure 2a), followed by a 750 ms presentation of a vertical line (126 mm (200 pixels)) (i.e., the landmark; at a different location across the horizontal line in each trial; Figure 2c). Locations of the vertical line were at (-25.2, -6.3, -3.1, -2.5, -1.8, -1.2, -0.6, 0 (center), 0.6, 1.2, 1.8, 2.5, 3.1, 6.3, 25.2 mm; -40, -10, -5, -4, -3, -2, -1 0, 1, 2, 3, 4, 5, 10, 40 pixels). To avoid aftereffects, a mask consisting of vertical lines was shown immediately after landmark presentation until the end of the trial. The participant indicated verbally whether the vertical line was located either to the *left* or *right* from the center of the screen. The experimenter pressed ‘A’ if the answer was ‘left’ and ‘L’ if the answer was right. Then the next trial started, for a total of 60 trials. Each of the 15 locations was presented 4 times in random order. Each participant’s data were fitted with a cumulative normal distribution function to generate estimates of the point of subjective equality (PSE) in Matlab; the location of the landmark where the participant was equally likely to determine it ‘left’ or ‘right’. The PSE, our primary outcome measure, was included in the analyses. The shift in PSE (before versus after the RHI) reflected the shift in space, hence peripersonal space. The duration of this task was about 10 to 15 minutes.

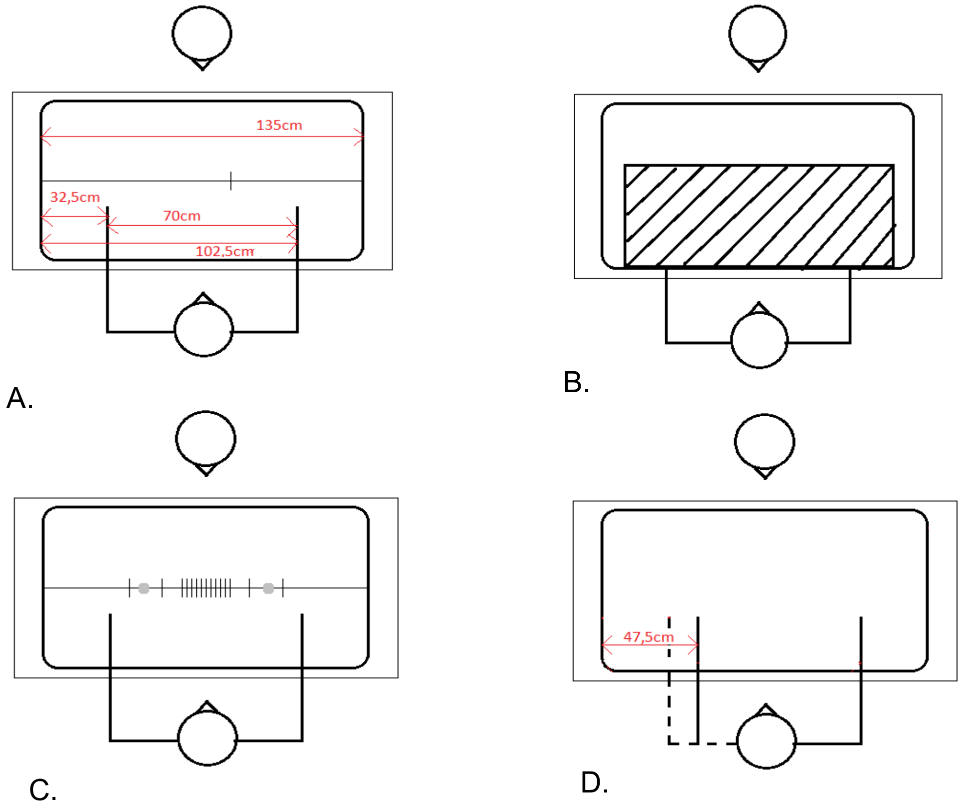


Figure 2. a. Experimental set-up (not drawn to scale) and dimensions for the landmark task, top=experimenter, bottom=participant, one trial of the landmark is shown. b. Set-up of proprioceptive drift with an occluder covering the lower arms c. All possible landmarks (not drawn to scale). Only one of these landmarks was shown each trial. Each trial started with a static dot (either left or right from the center of the screen) that disappeared when the landmark appeared. d. Hand positioning during the rubber hand illusion. Note that the dotted (real) arm was occluded by a black occluder. Only the added left rubber hand and the real right hand were visible to the participant.

Rubber hand illusion

After the first landmark session, the left arm was covered up by the occluder and RHI was set up, see Fig. 2d. While the participant had his eyes closed, the rubber hand was placed next to the real left hand in an anatomical congruent position, at a distance of 15cm to the right (Lloyd, 2007). To optimize the illusion, a cloth was placed over the shoulder of the participant. In the experimental condition, the illusion was established by stroking the index finger of the real and rubber hand simultaneously with a soft brush for 90s, while the participant was visually focusing on the rubber hand. In the other group, the asynchronous group, the stroking was asynchronous: first the rubber hand was touched and then the real hand. Location and velocity of stroking were held constant.

After inducing the illusion, the rubber hand was removed and both real hands were covered by the occluder (Figure 2b). The proprioceptive drift was now measured for the second time. This procedure was identical to pre-session. The occluder was then removed, so both hands were visible again, as in starting position (Figure 2a). Then the landmark task started for the second time with the exact same procedure as in the pre-illusion session. Thereafter, the straight-ahead pointing task was performed and again the procedure was identical to the pre-illusion session.

Embodiment questionnaire

To conclude the experiment, the participant filled out the Embodiment Questionnaire (Kammers et al., 2009). This questionnaire contained 10 items to measure the experience of the rubber hand illusion. For example: '*It seemed like the rubber hand was my own'* and '*It seemed like I had more than two hands'*. The participant responded on a 11-point Likert scale with 0=strongly disagree and 10=strongly agree. The overall duration of the experiment was about 40 minutes.

Analysis

For all our outcome-measures we used a Mixed ANOVA with *time* (pre-test versus post-test) as the within subject factor and synchrony (synchronous stroking versus asynchronous stroking) as between subjects factor. In addition, we also analyzed our data with a Bayesian mixed ANOVA, which uses a linear mixed model. We used Cauchy (uninformative) priors on effect size (Morey et al., 2016; Rouder et al., 2012). Thus, next to the frequentist approach we report Bayes factors which yields the probability of a model given the data (i.e., a certain combination of effects) relative to a null model (i.e., no effects), that is, values larger than 1 are in favor of H1. Bayes Factors (BF) that provide evidence in favor of the null model are abbreviated as BF_{01}, Bayes Factors that provide evidence in favor of a difference are abbreviated as BF_{10}. Since the Bayesian approach can quantify evidence for both directions (e.g., evidence for H1 *and* evidence for H0), it allows evaluating null effects, which is not the case in the classical frequentist approach (Morey et al., 2016).

RESULTS

Subjective ownership in the Synchronous stroking Group (SG) and Asynchronous stroking Group (AG).

In total we tested 65 participants (36 in the asynchronous stroking group and 29 in the synchronous stroking group). Shapiro Wilk test showed that data approximated a normal distribution, except the ownership scale (p<.001), all other *p-values* $\geq$ .154. Repeated measures ANOVA revealed a main effect of *subscale*, $F(1,63)=135.3$, $p< .001$, partial $\eta^2 =.683$, indicating a higher score for the ownership-subscale than the control-subscale (see Figure 3). There was also a between *groups*-effect, $F(1,63)=49.66$, $p< .001$, partial $\eta^2 =.441$, indicating a higher score for the SG than for the AG. Additionally, we found an interaction between *subscale* and *group* $F(1,63)=60,93$, $p< .001$, partial $\eta^2 =.492$. Similarly, Bayesian analyses revealed that the highest posterior model probability (P(M)=0.2, P(M|data)=5.969e+22) was for the model that included main effects for *subscale* and *group* and the interaction effect *subscale* x *group*, this was considered an extreme effect. *Post-hoc* Bonferroni corrected t- testing revealed that this interaction effect was driven by the difference between the ownership-scale of the SG and AG, $t(63)=-9.755$, p <.001 Cohen's d =-2.434 (BF_{10} = 1.42e+11, which is classified as extreme evidence in favor of a difference) and not the control subscale, $t(63) = -2.116$, p = .076 Cohen's d=-.528 (however BF_{10} = 1.64, which may be classified as slight anecdotal evidence *for* a difference).

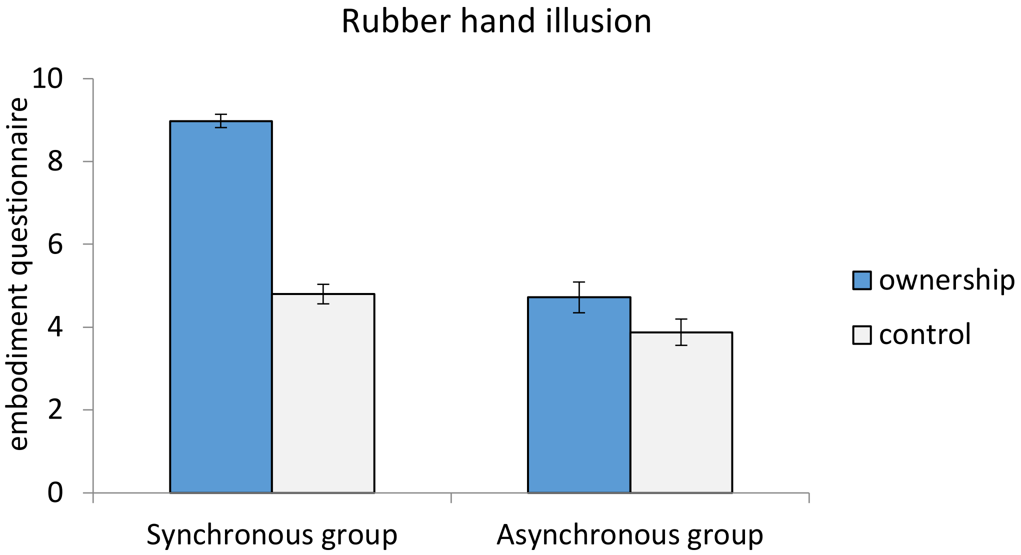


Figure 3. The data on the ownership questionnaire (see text for details). The panel shows the average score on the ownership scale (question 1-3) and control scale (question 4-10) for the Synchronous stroking Group and Asynchronous stroking Group. Error bars represent the standard error of the mean.

Proprioceptive drift (PD) for the SG and AG

For the proprioceptive drift Shapiro Wilk showed that all data, except for the pre-measure (*p*= .041) of the SG, approximated a normal distribution, all other *p-values* $\geq$ .235. Analyses revealed a main effect of time *F*(1,63)=13.161, *p*= .001, partial η^2 =.173, and an interaction of *time* (pre vs. post) x *group* (SG vs. AG) *F*(1,63)=8.713, *p*= .013, partial η^2 = .121 (see also Figure 4). Bayes analyses revealed that the highest posterior model probability (P(M)=0.2, P(M|data)=0.884) was for the model that included main effects for *time* and *group* and the interaction effect *time* x *group.* The Bayes Factor (BF$_{10}$) was 30588.791, which is considered as extreme evidence in favor of this model, indicating that the type of stroking (i.e., synchronously or asynchronously) had a differential impact on proprioceptive drift (inclusion Bayes factor for the interaction: 3715.825). To further test this, we applied both a Paired Samples T-test and a Bayesian Paired Samples T-test to compare the pre- and post-sessions for each group. Analyses revealed a significant difference between the pre- and post-session *t*(28)=-3.707 *p* < .001, Cohen's *d*=-.688, with a Bayes Factor of 36.099 for the SG, which is considered as very strong evidence for a difference (Suppl Figure 1). As expected for the AG, the pre- and post-session did not differ, *t*(35)=-.0622 *p*=.538, Cohen's *d*=-.104. The Bayes Factor was 0.214 indicating moderate evidence *against* a difference between the pre- and post-test. Results revealed that participants indeed drifted proprioceptively towards the rubber hand after synchronous stroking, indicating the RHI was well induced.

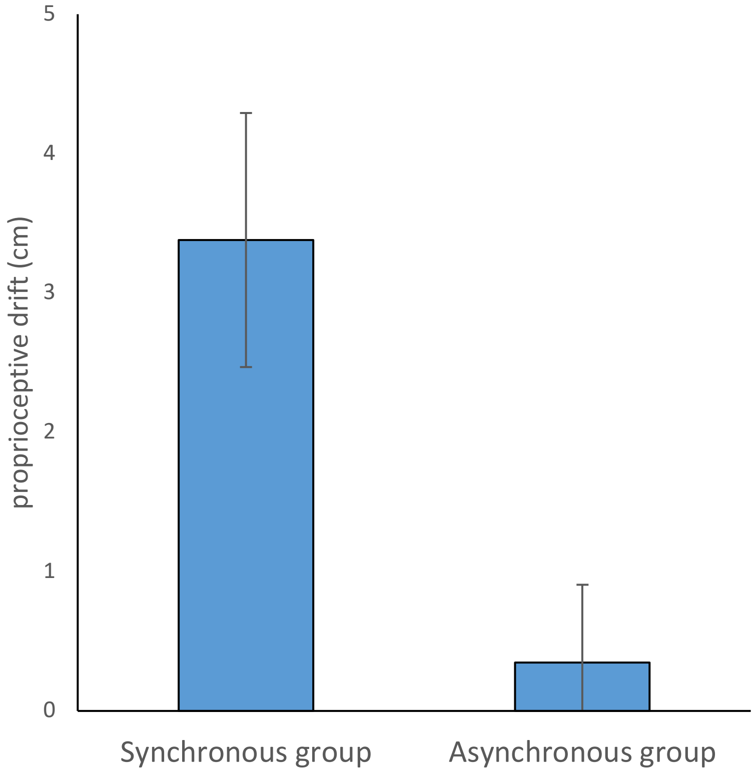


Figure 4. Average estimates in cm of proprioceptive measure (i.e., difference between pre- and post-illusion) for the synchronous stroking and asynchronous stroking groups for the left index finger. Error bars represent standard error of the mean.

Landmark task in the SG and AG

The data of each individual participant was fitted using a cumulative normal distribution function to generate estimates of the point of subjective equality. Overall, the R^2 showed a reasonable to good fit (SG mean $R^2 = 0.69$ pre-illusion; mean $R^2 = 0.70$ post-illusion; AG: mean $R^2 = 0.68$ pre-illusion; mean $R^2 = 0.67$ post-illusion). The landmark estimates (i.e, PSE) were analyzed using both a mixed ANOVA and a Bayesian Mixed ANOVA with *time* (pre versus post) x group (synchronous versus asynchronous) mixed ANOVA.

Shapiro Wilk test showed that data was normally distributed, all $p \geq .235$. A mixed ANOVA revealed a main effect of *time* $F(1,63)=14.951$, $p< .001$, partial $\eta^2 =.184$, and a near significant interaction between *time* and *group* $F(1,63)=3.219$, $p= .078$, partial $\eta^2=.049$ (see also Figure 5). Bayesian analyses revealed the highest posterior model probability (P(M)=0.2, P(M|data)=0.423) was for the model that only included the main effect of *time* ($BF_{10} = 45.583$). The BF_{10} for the model that included all the effects (main and interaction) was 15.664, which is still considered as strong evidence in favor of this model, however it is not the best model given the data. We however decided to apply subsequent t-tests to compare the average PSE of the participants before the RHI to the average PSE after the RHI in the SG, and the AG. This difference between the pre- and post-session was only statistically significant for the SG, *t* (28)=-3.653 *p* = .001, Cohen's *d*=.678 (BF_{10} = 31.879, which is classified as very strong evidence in favor of a difference between pre- and post), but not for the AG, *t*(35)=-1.606, *p* =.117 Cohen's *d*=.268 (BF_{10} = .576, which is classified as anecdotal evidence in favor of an effect between pre-and post; see Suppl Figure 2).

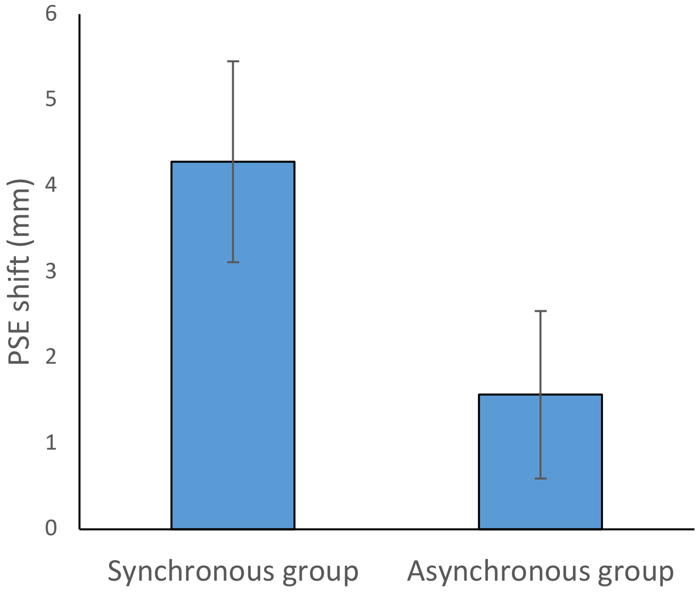


Figure 5. Average shifts in point of subjective equality (PSE) on the landmark task (i.e., difference between pre- and post-illusion) for the synchronous stroking and asynchronous stroking groups. The PSE is depicted in mm for convenience but has been analyzed in pixels. The error bars depict the standard error of the mean.

Straight ahead pointing for the SG and AG

As the position of the left hand was influenced by the RHI, we only analysed the data for SAP for the right hand. Shapiro Wilk test showed that data was not normally distributed for both the pre- and post-session of the AG (*p* = .009, and p=. 047, respectively), and for the post condition of the SG (p=.005). Wilcoxon signed rank test showed a significant difference between pre- and post-illusion SAP for the SG group *Z* = -2.76, *p* = .006 (see also Figure 6). This difference was not significant for the AG group, *Z* = -1.53, p=.13. Bayesian analyses (see suppl fig 3) revealed moderate evidence in favor of a pre- post difference for the SG (BF_{10} =6.39) and anecdotal evidence in favor of the H0 hypothesis for the AG (BF_{01}=2.786).

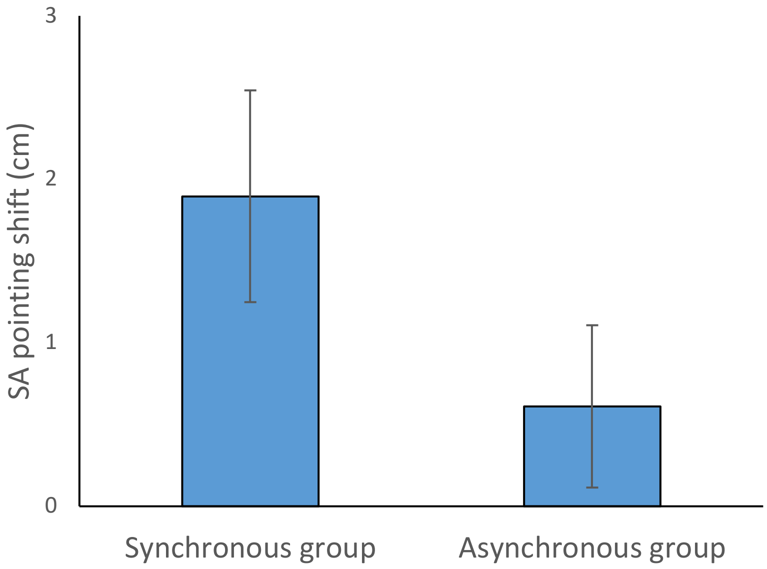


Figure 6. Average shifts in pointing straight ahead (i.e., difference between pre- and post-illusion) for the synchronous stroking and asynchronous stroking groups. The error bars depict the standard error of the mean.

All in all, we find a significant shift in peripersonal space (i.e., shift in PSE) to the right only after synchronous stroking. This shift to the right is also apparent in the proprioceptive drift and in straight ahead pointing task. Our next step was to test whether our primary outcome measure, the PSE, which reflected perception of the peripersonal space, correlated with any of the secondary outcome measures. In the next paragraph, we tested whether the shift in space was driven by feelings of ownership (ownership-scale of the questionnaire), proprioceptive drift, and lastly if the shift in space also correlated with a shift in subjective body midline.

Correlations between the shift in PSE, subjective ownership, shift in proprioceptive drift, and shift in straight ahead pointing.

All participants (SG and AG together) were used to test whether there was a relation between the shift in the PSE (pre-post) and subjective ownership, proprioceptive drift (post-pre) for the left hand, and straight-ahead pointing (pre-post) with the right hand. The ownership scale, the proprioceptive drift (post-pre) and straight-ahead pointing (pre-post) deviated from normality ($p < .001$; $p = .014$ and $p = .006$ respectively), the shift in PSE was normally distributed $p \geq .316$. Kendall's tau statistic was used for all the data. We found a significant correlation between the shift in PSE and the shift in the proprioceptive drift, $\tau_b = .239$, $p = .007$, indicating that the larger the proprioceptive drift towards the rubber hand (i.e., shift towards the right), the more the participants shifted to the right in space. Analyses also revealed a significant correlation between the shift in PSE and the shift in body midline as indicated with the right-hand SAP τ_b = .235, *p* = .007, indicating that the shift in space to the right was related to a rightward shift in the subjective midline on the body. Analyses did not reveal a significant correlation between the shift in PSE and subjective feelings of ownership τ_b = .146, *p* = .094. Intriguingly, subjective ownership did not correlate to the shift in PSE, but was significantly correlated to the proprioceptive drift, τ_b = .242, *p* = .007. Furthermore, while proprioceptive drift and SAP were both significantly correlated with a shift in PSE, they did not correlate with each other, τ_b = .109, *p* = .224.

DISCUSSION

In the current study we aimed to test the flexibility of our peripersonal space with the rubber hand illusion. Specifically, we tested whether performance on the landmark task can be modulated by a change in ownership caused by the rubber hand illusion. To investigate this question, two groups of participants performed a landmark test *before* and *after* the RHI (e.g., 90s of multisensory stimulation). The landmark task required the participant to indicate whether a transection mark was located to the left or right of the center of a screen. We divided our participants in two groups; one group experienced synchronous stroking on the left hand, and the other group experienced asynchronous stroking on the left hand. We expected that the bias on the landmark task to be shifted to the right as a consequence of feeling ownership over a left rubber hand. We indeed found a shift to the right in PSE following illusion induction, and only for the ‘synchronous stroking’ group. These findings concur with previous findings of Ocklenburg et al. (2012). In a somewhat different experiment, Ocklenburg et al. (2012) found that “high responders” (e.g., individuals who experienced the RHI vividly) as opposed to low responders (e.g., individuals who reported a low illusion score) shifted (i.e., the perceived space) to the right on a line bisection task after left-sided RHI. The line bisection task is slightly different from the landmark task, as it requires an active motor response, but the rationales of the tasks are very similar; both represent a shift in space. The authors suggest that for the high responders the rubber hand was integrated in their body image, which was not the case for low-responders. In comparison to Ocklenburg et al., (2012) the shift that we observed was similar, albeit slightly smaller in magnitude. We believe that the magnitude of our shift was attenuated by the duration of inducing the illusion, which was only 90s, relatively short compared to Ocklenburg and colleagues (2012) 180s. Also, in their study, the Line Bisection task followed the inducement of the illusion immediately, and in our design, we first measured the proprioceptive drift for both hands and thereafter we performed the landmark for ten minutes. In hindsight, we believe that the set-up of our post-illusion landmark-task also attenuated the effects: We now kept the pre- and post-landmark-measures identical, so if we would find an effect (i.e., shift in PSE) it could only be attributed to the type of stroking. Although this is probably the case, viewing your own right hand, however, in the post-landmark task might have provided visual feedback of one's body midline, and consequently decreased the magnitude of the rightward shift in space. Finally, another difference between our study and that of Ocklenburg et al. (2012) is that we used synchronous and asynchronous stroking in two different groups to induce differences in ownership over the rubber hand, while Ocklenburg depended on individual difference in sensitivity to the RHI to make two groups. As a consequence, it is likely that our synchronous group contains individuals who did not experience ownership over the RHI and this may have resulted in smaller effects on the landmark task. Nevertheless, overall, there was a robust difference in RHI effects on the questionnaires and proprioceptive drift between the two groups.

It seems warranted that changes in the representation of the body (e.g., embodying a new rubber hand) can, at least transiently, change how the space surrounding the body (the peripersonal space) is perceived. Literature suggests a close and dynamic relationship between the two representations at a neural and behavioral level. These accounts were first demonstrated at a neural level in monkeys; bimodal neurons in the multisensory brain areas (e.g., premotor and parietal areas) respond to both tactile stimuli *on* the monkey's limb and visual stimuli *nearby* the limb (Graziano et al., 1997; Rizzolatti et al., 1981a, 1981b). Numerous behavioral studies in humans using different kinds of bodily illusions have found that spatial characteristics of peripersonal space can be modulated and that boundaries can be extended to include a fake or virtual arm (Aspell et al., 2009; Guterstam et al., 2015; Maister et al., 2015; Pavani et al., 2000; Zopf et al., 2010). The general idea is that embodying a fake arm after multisensory stimulation can alter the spatial features of the receptive fields of multisensory neurons in such a way that now the fake or virtual body part is included in the body image (see Blanke et al., 2015) for an insightful discussion on this topic). Although we are not measuring the boundaries of peripersonal space per se, our set up differs slightly from the studies just mentioned, we do believe that if an arm is integrated in the body representation, it can shift the perceived body space and objects presented in that body space.

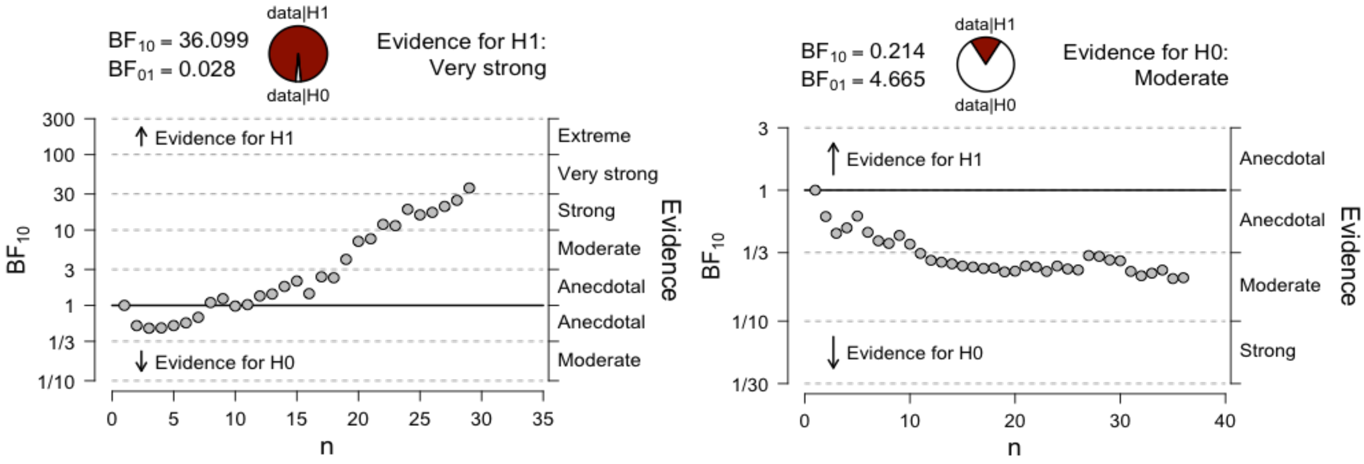
Intriguingly, the right-warded shift was not related to the subjective feeling of ownership, thus more explicit accounts (e.g., via a questionnaire) of experienced body ownership per se do not drive these changes in space. However, the shift in space was related to proprioceptive drift, which is an implicit measure of the shift from the real to the artificial hand and to a shift in pointing straight ahead with the non-illusion right hand. During the proprioceptive drift, the visual input becomes more dominant than the proprioceptive input. In order for our brain to reconcile this, the visual dominance shifts the perceived localization towards the *seen* rubber hand (Pavani et al., 2000), and thus distorts our position sense. The term 'dominant' might be misleading here, since especially adults (as opposed to young children) integrate *all* the incoming senses in an optimal way or "statistical optimal fashion", i.e., weigh the reliability of visual, proprioceptive and tactile signals in a given task (Ernst & Banks, 2002). Moreover, adults seem to give more weight to visual input in the horizontal direction (i.e., left/right), while more weight is given to proprioception in depth perception (i.e., near/far) (Snijders et al., 2007; van Beers et al., 2002), commonly referred to as the direction dependent weighing account (Snijders et al., 2007). The finding that this shift in proprioceptive drift in our study correlates to our shift in space (e.g., PSE) is then not surprising: both underlying mechanisms of these outcome measures are visuo-spatial in nature (and showed a shift from left to right).

In contrast, the questionnaire is a more indirect and cognitive measure. Thus, we found a correlation between the shift in PSE and the proprioceptive drift, but no correlation between the shift in PSE and the ownership questionnaire. One would conclude that the drift and the ownership questionnaire then measure different aspects of body ownership. However, we actually did find a correlation between the questionnaire and the proprioceptive drift, indicating overlap between the underlying mechanisms. Recent accounts (Tajima et al., 2015) using the mirror illusion also concluded that the "same integration or matching processes between visual and proprioceptive feedback could be used to evoke proprioceptive drift, feeling of ownership, and agency", although see Rohde et al. (2011) for a discussion on the dissociation between subjective ownership and proprioceptive drift. Thus, some overlap is required between the underlying mechanisms of these measures, but they were not equally related to the shift we found in peripersonal space. To what extent and in what way they do overlap remains inconclusive (Tajima et al., 2015).

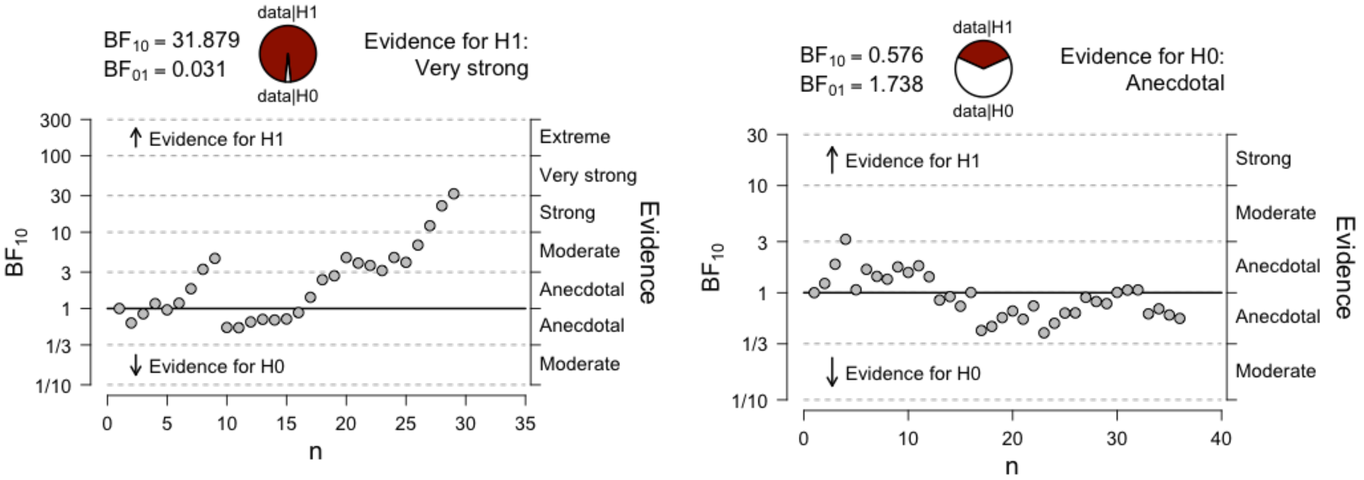
Another contributing factor to the shift in PSE on the landmark task, appears to be the perception of the subjective body midline. In his study on the effect of the RHI on pseudoneglect, Ocklenburg et al. (2012) suggested that the shift in line bisections might be related to a shift in subjective experience of this body midline. This idea was assessed in the current study using the straight-ahead pointing task. Indeed, we found that the subjective body midline had shifted more to the right in the SG compared to the AG. Moreover, overall, the shift in straight-ahead pointing following the illusion also correlated with the shift in space as measured using the landmark task. Both these findings are consistent with the idea that the RHI induces a shift in subjective perception of the body midline, which affects perception of space around the body. However, intriguingly, while both the proprioceptive drift in left hand location and the change pointing straight-ahead (using the non-illusion right hand) were correlated with the change in PSE on the landmark task, they did not correlate with each other. This suggests that the shift in subjective body midline is not necessarily linked to the change in perceived left-hand position following the RHI. Rather, the RHI might affect the spatial representation that is linked to the proprioceptive localization of the hands (i.e., hand-centered) and that of the torso (the subjective midline (e.g., straight-ahead judgments) independently and both contribute to a shift in perceived landmark location. Future studies should confirm this idea.

To conclude, the present study, combined with previous studies indicates that changes in bodily processing can modulate the perceived space around the body. This change seems to stem from a shift in proprioceptive localization, rather than subjective feelings of ownership and from a change in subjective body midline. The findings presented in this manuscript are of particular interest for certain groups where proprioceptive input is compromised, which frequently occurs after stroke (Winward et al., 2002). Our results suggest that not only bodily information will be differentially processed (i.e., suboptimal multisensory integration) as was recently found (Llorens et al., 2017; White & Aimola Davies, 2017), but also the space around the body. Future studies should thus also focus whether the region around the body is impacted by disturbances in body ownership.

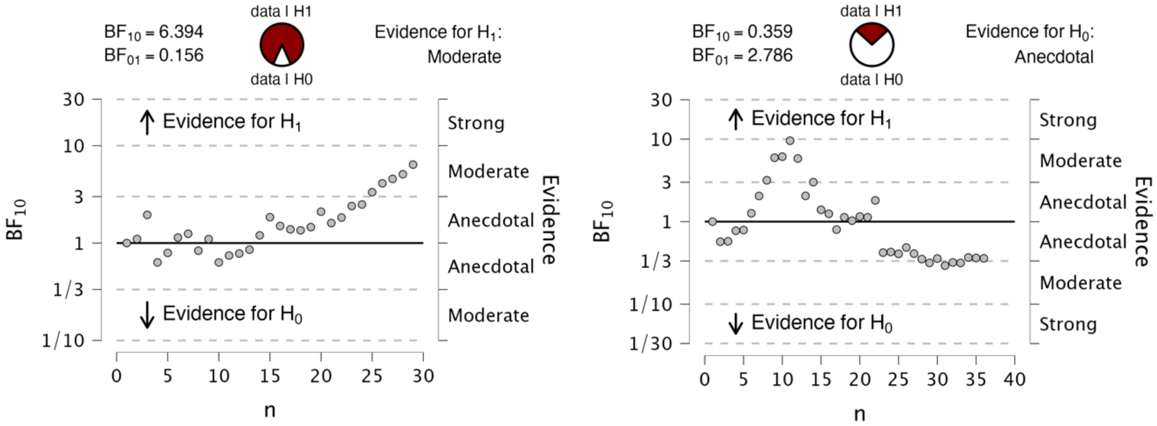
SUPPLEMENTARY FIGURES.



Supplementary figure 1. Sequential plots for the synchronous stroking group (left panel) and the asynchronous stroking group (right panel) for proprioceptive drift. The current n provides very strong evidence in favor of the alternative hypothesis (H1; a difference between pre and post) in the synchronous group, whereas evidence was moderate against a difference (H0) between the pre- and post-session in the asynchronous stroking group.



Suppl Figure 2. Sequential plots for the synchronous stroking group (left panel) and the asynchronous stroking group (right panel) for the landmark task. The current n provides very strong evidence in favor of the alternative hypothesis (H1; implying a difference between pre- and post-session) in the synchronous group, whereas evidence is anecdotal in favor of no difference between the pre- and post-session in the asynchronous stroking.



Suppl figure 3. Sequential plots for the SG (left panel) and the SG (right panel) for straight ahead pointing. The current n provides moderate evidence in favor of the alternative hypothesis (H1; implying a difference between pre- and post-session) in the synchronous group, whereas evidence is anecdotal in favor of no difference between the pre- and post-session in the asynchronous group.

Chapter 5

The contribution of different afferent signals to the perceived shape of the hand

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ABSTRACT

Research has shown that the perceived representation of the hands is highly distorted, featuring shortened fingers and broadened hands. This pattern of distortion matches the geometry and tactile acuity of the receptive field on the dorsum side of the hand. The degree of distortions appears to depend on the sensory information available. Our aim is to test whether the perceived hand representation can be differentially modulated, i.e., we examined the sensory contributions of different afferent signals (proprioception, touch, movement) to the implicit hand representation.

Twenty-three healthy individuals participated in this study. We administered an adapted version of a body localization task to induce an implicit representation of the hand. Sensory signals were manipulated in four different conditions: a proprioceptive condition (hand still under monitor), a touch condition (i.e., touch on finger), a movement condition (i.e., movement of finger), and an imagine condition (i.e., absence of the hand).

We replicated previous reports on hand distortions consisting of width overestimations and length underestimations. Similarly, the overall aspect ratio concurred with previous findings; participants perceived their hand wider than it is long. The overall shape seems robust across conditions, although when modulated by a movement, the perceived distortions became slightly more apparent. Generally, our results imply that the implicit representation of our body relies on a stored body-model, which seems unaffected by different sensory input.

INTRODUCTION

Research has shown that the perceived representation of the hands are highly distorted, featuring shortened fingers and broadened hands (Longo & Haggard 2010, Longo et al., 2012; Longo, Mattioni, & Ganea, 2015; Saulton et al., 2015; Saulton et al., 2016, Coelho et al., 2016) and this has also recently been found for the lower limbs (Stone et al., 2018). For the hands, this pattern of distortion matches the geometry and tactile acuity of the receptive field on the dorsum side of the hand. These receptive fields are oval-shaped (Powell and Mountcastle, 1959; Brown et al., 1975), hence, there are more receptive field boundaries mediolaterally than proximodistally, and therefore we perceive the overall shape of the hand to be wider than it is long.

Intriguingly, the degree of distortion appears to rely upon the dominant sensory information available. In a hand localization task (originally developed by Longo et al., 2010 and adapted by many others such as Saulton et al., (2015), Saulton et al., (2016); Coelho et al., (2016)) participants had to report the felt location of the tip or knuckle of the fingers of their hand, which was occluded by a monitor. Here, only proprioceptive information was available, and participants typically perceived a highly distorted hand: broadened (20 - 80%) and shortened (20 - 40%) compared to their actual hand (Longo & Haggard, 2010, Longo & Haggard, 2012; Longo et al., 2015; Saulton et al., 2015; Saulton et al., 2016, Coelho et al., 2016). Likewise, when participants had to make tactile distance judgments, the pattern of distortions was similar; the distances for the tactile stimuli mediolaterally were consistently perceived as larger (30%-40%) than proximodistally (Longo & Haggard, 2011). However, in a task where participants had to visually match a template hand to their own hand, participants were highly accurate and perceived their body as near-veridical (Longo & Haggard, 2010; Saulton et al., 2015). Different types of sensory input do appear to have some influence on these distortions, although they do not alter the nature of these distortions (e.g., shorter fingers and wider hand width). This is true for tactile input (Longo, 2017; Longo, Mancini, & Haggard, 2015; Longo & Morcom, 2016; Mattioni & Longo, 2014), noninformative visual input about where the participants were pointing (but not of the hand to which they were pointing) (Longo, 2014). However, changing proprioceptive input appears to have a more substantial influence. Longo (2015) showed that spreading the fingers apart resulted in increased hand width and finger length perception in comparison to fingers placed together. Even non hand related vestibular input can influence hand localization performance, with caloric stimulation resulting in larger perceived hand length and width (Lopez, Schreyer, Preuss, & Mast, 2012), although this was not found in another study using galvanic stimulation (Ferre, Vagnoni, & Haggard, 2013).

Thus, sensory afferents appear to be used to generate information about our body (e.g., length of our fingers). However, there is no direct link between specific afferent input and the representation of that body part; that is, a single touch, or proprioceptive information by itself does not give us information about the metrics of our body. How then, do we infer the size of our body? Longo proposed a model in which immediate afferent signals are linked to stored representations of the body, the so-called body model (Longo, Azañón, & Haggard, 2010). Following this line of reasoning, accurate tactile size perception and proprioceptive perception requires referencing to a mental body model that includes the size and shape of body parts. Thus, perceived tactile or proprioceptive distance is shaped by implicit, low-level, somatosensory organization as well as more explicit, higher order models of our body (Longo., 2015). Indeed, Longo & Haggard (2012) showed a similar, albeit reduced distortion for the palm of the hand, compared to the back of the hand. The distortions for the palm and back of the hand were also highly correlated. As the tactile receptive fields of the palm of the hand are more symmetrical, this suggests that the distortion is not just determined by low level receptive field properties, but also by an integrated 3D representation of the hand. Further evidence for the importance of a stored representation of the hand comes from the study by Longo et al. (2012) who measured the constructed hand map of the phantom hand in an individual with a congenital absence of that hand. The map showed similar distortions to that of the physical other hand and those found in previous studies. Thus, the degree of distortions appears to depend on both the sensory information available as well as more cognitive top-down effects.

While different sensory manipulations have been investigated in separate studies, so far, their specific contribution has not yet been compared within one study and one group of participants. Our aim therefore is to test whether the perceived hand representation can be differentially modulated within the same group of individuals, i.e., we directly compared the sensory contribution of different afferent signals (proprioception, touch, movement) to the perceived implicit hand representation. This is of particular interest for when sensory information becomes absent, for instance after stroke when somatosensory, proprioceptive and motor signals can be (selectively) impaired. For these patients there is no or diminished sensory referral to the body model and above that, the lesion might affect he body model itself.

As discussed, it is clear from literature (Longo, 2017; Longo et al., 2015; Longo & Morcom, 2016; Mattioni & Longo, 2014) (Longo et al., 2010, Longo et al., 2011; Longo et al., 2012; Longo et al., 2015; Saulton et al., 2015; Saulton et al., 2016, Coelho et al., 2016) that both tactile and proprioceptive afferents, which are combined with a stored body model representing size and shape, have highly distorted representations when either one of them is being modulated. No information is available, however, on how we perceive our hand representation after a movement. This might generate a different representation than when only proprioceptive information is present, since movement is linked to multiple sources of information, such as information from muscle and joint receptors (Proske et al., 1988). In addition, the brain also generates a copy of the motor-output, an "efference copy" (which initiates from the motor cortex) of the movement itself (Sperry, 1950).

Thus, in the current study we manipulated the sensory information available (proprioception, touch, movement or no input (i.e., imagination) in order to investigate their differential contribution to the perceived size and shape of the hand. For this we used an adapted version of the body localization task that Saulton (2015 & 2016) used.

METHODS

Participants

A priori power analysis suggested that with power set at 0.8, effect size of 0.5 (Cohens '*d*'; effect size *F* = 0.25), and statistical significance set at 0.05, the current study required 24 participants. Inclusion criteria were healthy participants with no psychological/psychiatric disturbance in the past year, and no primary somatosensory and motor problems in the upper extremities. In total, 26 participants were tested, and three were excluded, resulting in 23 included participants (21 female). The first participant was excluded because she reported diminished somatosensory feeling due to low body temperature. The second excluded participant had difficulties differentiating between the fingers (i.e., consistently mixed up the index-, middle- and ring finger), and could therefore not follow instructions. The third participant did not follow instructions in the touch condition and was therefore considered an outlier. Data was not stored of the first participant; she was retested two weeks later. Mean age of the final inclusion was 26.9 (SD 8.8), and most people were right handed (average laterality quotient 70.1(53.2)[2]. All participants gave written informed consent to participate and received money as compensation for their time. The study was approved by the local ethics committe and conducted in accordance with the guidelines of the local ethical board and the declaration of Helsinki.

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[2] Range laterality quotients: Left-handed between -1 and -100; Right-handed between 1 and 100; Extreme handed include sinistrals between -80 and -100 and dextrals between 80 and 100; Mixed handed between -79 and 79.

Experimental design and set-up

The experimental set-up consisted of a horizontally tilted (17inch, resolution 1024 x 768) monitor (dimensions width/length; 38/30.5 centimeters (cm)), which was placed on a stand 15 cm above the top of the table (Figure 1a). The left hand of the participant was placed on a template hand below the monitor. The middle finger was always positioned 20.5 cm from the left side of the monitor, the fingertip of the middle finger 11 cm from the top of the monitor.

The experiment consisted of four conditions in a within subjects design, that is, participants performed - in random order - the following conditions: proprioceptive, imagine, touch, and movement (see ‘procedure/task’ for details). In each condition participants had to click to indicate the *felt* position of one of the ten landmarks (i.e., either knuckle or fingertip of one of the 5 fingers, Figure 1b) on a black screen. This landmark was presented (one at a time) in text (e.g., “knuckle ring finger”) at the top of the screen in random order. In order to prevent feedback of a previous mouse-click, the cursor jumped after each click to a random y-coordinate at the right side of the screen. Each landmark (10 in total) was tested 5 times in random order, resulting in a total of 50 trials per condition.

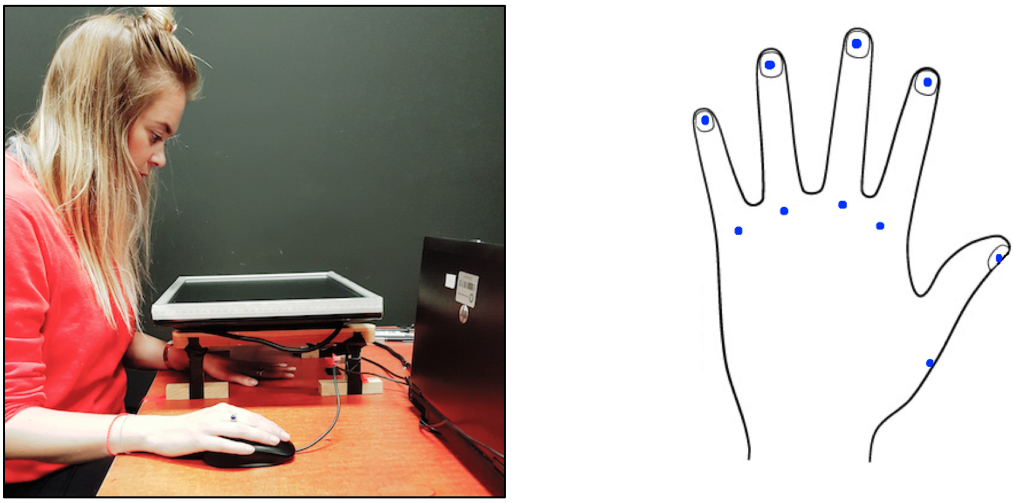

Figure 1a. Experimental set-up. 1b. Blue marks indicate the landmarks for the hand localization task, from left to right; tip and knuckle of each finger (i.e., little finger, ring finger, middle finger, index finger, and – thumb).

Procedure body localization task

Prior to the experiment informed consent and demographic information was obtained. Consequently, participants were informed that the experiment aimed at investigating the hand representation, and that they – when the own hand was placed below a monitor - had to click with a mouse at the felt position of a visually presented landmark (e.g., “tip of the index finger”). Prior to the experiment participants were familiarized with the 10 landmarks, that is, they had to point at the landmark (on their actual hand), either knuckle or tip, of the finger that was named by the experimenter in random order. When the participant pointed at an incorrect landmark, the procedure was repeated until all ten landmarks were pointed at correctly. Subsequently, the left hand was placed below the monitor and instructions were given for all four conditions. For the proprioceptive condition participants were instructed to click with the mouse (showing a white cursor on screen) at the felt position of the landmark. In the imagine condition, participants had to imagine their hand was still below the screen and had to click where they imagined the landmark would be. During this condition their left hand was at a comfortable place, mostly their lap. In the touch condition, the participant was touched briefly with a brush on the intermediate phalange of the finger (in longitudinal direction) by the experimenter, the participant still had to click at the felt position of the visually presented landmark. In the movement condition, the participant briefly moved their finger up and down and also had to click at the felt position of the visually presented landmark. In all but the movement condition, participants were asked to keep their left hand as still as possible. Prior to the actual experiment participants received 20 practice trials wherein they practiced all conditions (5 trials per condition), or more if necessary (i.e., participants did not understand the condition, clicked at one location only or randomly). In both the practice and experimental trials participants placed their left hand below the monitor and started with one of the 4 conditions in random order. After the task the actual measures of the hand were obtained. The whole test-procedure took one hour.

Analyses

The first outcome measure was the percentage of mis-estimation for the width of the hand and for the length of the hand separately. The perceived size of the length of the finger was based on the clicked x and y coordinates of the tip of the finger and the knuckle at the base of that particular finger. The perceived width was based on the clicked x and y coordinates of the knuckle of the little finger and the knuckle of the index finger (similar to Longo et al., 2010, Saulton 2015, 2016). In order to calculate the distance between the index finger tip with respect to the knuckle, the relative distance between the x-y coordinates of the knuckle and the tip of the index finger were calculated with the following equation:

$$distance = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2}$$

Once the displacement was calculated for each body part, the value was converted into mm. One pixel at the screen was .38 millimeters (mm). Then the percentage mis-estimation with respect to the actual size was calculated:

$$percentage\ of\ misestimation = \frac{perceived\ size - actual\ size}{actual\ size}\ x\ 100$$

A positive value (when different from zero) indicates an overestimation of a particular body part with respect to its actual size; a negative value indicates an underestimation.

The shape index, the second outcome measure, reflects the overall aspect ratio of the hand, which takes both length and width into account. First, we calculated the shape indices for both the actual and perceived hand separately with the following formula:

$$shape\ index\ (SI) = \frac{width\ hand}{length\ (middle\ finger)}\ x\ 100$$

Subsequently, for interpretation convenience and comparison with previous literature, we normalized the shape index with the following formula.

$$normalized\ SI\ (NSI) = \frac{perceived\ SI}{actual\ SI}$$

A NSI of 1 means a perfect score, that is, a veridical shape of the hand. When the NSI is >1, participants perceived their hand to be wider than it is long. When the NSI is <1, participants perceived their hand to be longer than it is wide.

RESULTS

First, we report whether the perceived estimations differed from the actual estimations for the *width*, reflected by a percentage misestimation. Second, we discuss whether the perceived estimation of the width was impacted by differential sensory signals (i.e., proprioception, imagine, touch or movement). The same analyses were done for the *length* of the fingers. Lastly, we report analyses on the comparison of the perceived versus actual *shape of the hand* (i.e., shape indices), and whether there was a difference in perceived shape *between* sensory conditions.

Overall, our data approximated normality; we therefore used parametric tests (i.e., Repeated measures ANOVA) most of the time. The data of the second outcome measure (shape indices) were not normally distributed; as a consequence, we used nonparametric tests (Friedman ANOVA) and present boxplots (medians). All p-values of post-hoc tests were corrected (bonferroni (hereafter *pbonf*)) for multiple (i.e., six) comparisons. If not stated otherwise, alpha levels of .05 (two-tailed) were used for the statistical tests.

Actual versus perceived estimations for the width

Since our data approximated a normal distribution, (except proprioceptive condition (p = .038)), parametric tests were used. One sample T-Tests revealed a significant difference for all conditions (i.e., proprioceptive, imagine, touch and movement) from zero (all p-values < .001). As can be seen in Figure 2, a positive value was found for all conditions, which indicates an overestimation of the width of the hand.

Differences in perceived width between conditions.

Mauchley's test indicated that data violated the assumption of sphericity (p = .034), therefore degrees of freedom were corrected using Greenhouse-Geisser (ε =.732). Repeated measures ANOVA revealed an effect of condition, F (2.196, 48.306) = 4.391, p = .007, η^2 = .166. Follow-up comparisons revealed only a significant difference between the proprioceptive and movement condition, t (22) = -3.580, p = .010 (*pbonf*). Other comparisons did not reach significance, all follow-up t-tests summarized: < -2.472, p > .130 (*pbonf*).

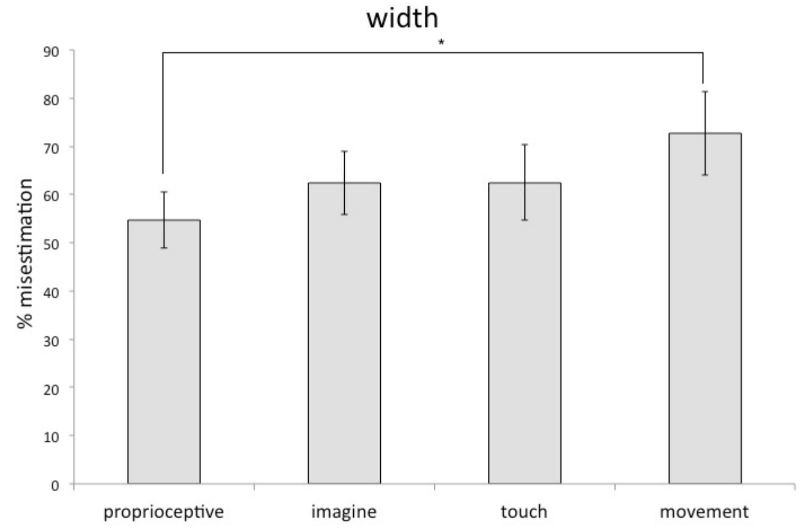

Figure 2. Percentage misestimation for the width of the hand for the conditions proprioceptive, imagine, touch, movement. Top line indicates a significant difference between the proprioceptive and the movement condition. Error bars represent standard error of the mean.

Actual versus perceived estimations for the length

For the length, data also approximated normality, only the little-, ring- and index finger in the movement condition deviated from normality, *p* = .026, *p* = .018 *p* = .038 respectively. The data of the other fingers in the movement condition, *and* all the data in the proprioceptive and imagine condition were normally distributed, therefore parametric tests were used. One sample T-Tests revealed a significant (all *p*-values < .001, except for the thumb in the touch condition *p* = .005) difference from zero for all fingers (i.e., little-, ring-, middle-, index finger and thumb) in every condition (i.e., proprioceptive, imagine, touch and movement). As can be seen in Figure 3, a negative value indicates an underestimation of the actual length.

Differences in length between conditions

Repeated measures ANOVA revealed a main effect of condition, *F* (3, 66) = 4.391, *p* = .015, η^2 = .166. Mauchley's test indicated that data violated the assumption of sphericity (*p* = .034), therefore degrees of freedom are corrected using Greenhouse-Geisser (ε =.621) for the main effect of finger, *F* (2.483, 54.628) = 46.074, *p* < .001, η^2 = .677. There was no interaction between condition and finger, Greenhouse-Geisser correction (ε =.418), *F* (5.014, 110.301) = 1.009, *p* = .416, η^2 = .044.

Follow-up comparisons for the main effect of *condition* revealed that the lengths of the fingers were significantly less underestimated in the *touch* condition, as opposed to the other conditions, (Figure 3); both movement and imagine conditions vs. touch $p < .001$ (*pbonf*), touch vs. proprioception $p = .017$ (*pbonf*). There was also a trend towards significance for the difference between the proprioceptive and the movement condition .070 (*pbonf*), other comparisons did not reach significance: proprioceptive vs. imagine $p = 1.000$ (*pbonf*), imagine vs. movement $p = .538$ (*pbonf*).

Follow-up comparisons for the main effect of *finger* showed that the ring finger was significantly more underestimated than all other fingers, all comparisons $p < .001$ (*pbonf*), whereas the thumb was the least underestimated compared to the other fingers (Figure 3), all comparisons $p <. 001$ (*pbonf*). Other comparisons were not significantly different, all $p > .471$ (*pbonf).*

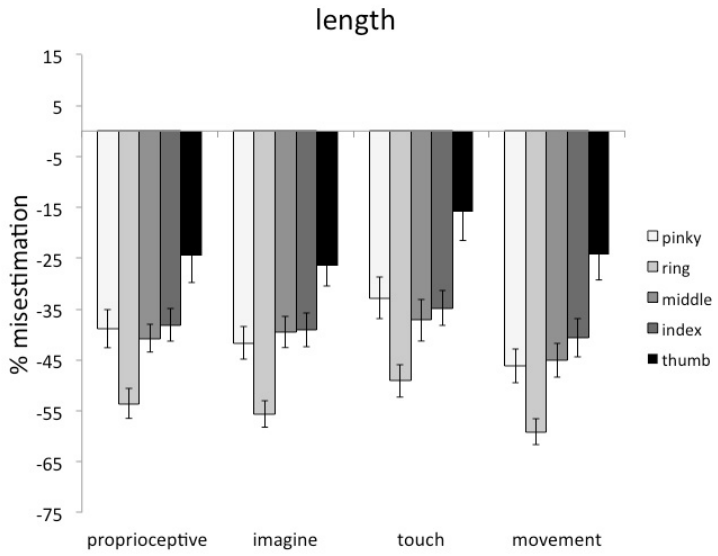

Figure 3. Percentage misestimation for the length of the hand for the conditions proprioceptive, imagine, touch, movement. Error bars represent standard error of the mean.

Actual versus perceived estimations: the normalized shape indices

Most of the data of the NSI deviated from a normal distribution: NSI proprioceptive ($p = .061$), NSI imagine ($p = .038$), NSI touch ($p < .001$) and NSI movement ($p < .001$). Wilcoxon Signed Rank Tests revealed that all NSI's were significantly different from 1, all comparisons $p = .001$. As can be seen in Figure 4 NSI's were larger than 1, indicating that, on average, participants perceived their hand to be wider than it is long.

Differences in the normalized shape indices between conditions.

In order to test whether differences *between* conditions were present, we applied a Friedman test. Analyses revealed a near significant effect of condition $\chi 2$ (3) = 7.75, *p* = .052. We still followed-up with pairwise comparisons, these analyses revealed only a significant difference between the proprioceptive and movement condition, *Z* = 2.85, *p* = .036 (*pbonf*). Noteworthily, the imagine condition (i.e., hand was not below the monitor) did not differ from the proprioceptive condition (i.e., when the hand was there), Z= 1.07, *p* = 1.000 (*pbonf*). Other comparisons did not reach significance either, all comparisons summarized Z < 1.78, *p* = .48 (*pbonf*). Thus, the overall shape (i.e., distortion of the hand) does not differ between the proprioceptive, imagine, touch condition), however when participants made a movement with their finger, distortions become slightly more apparent.

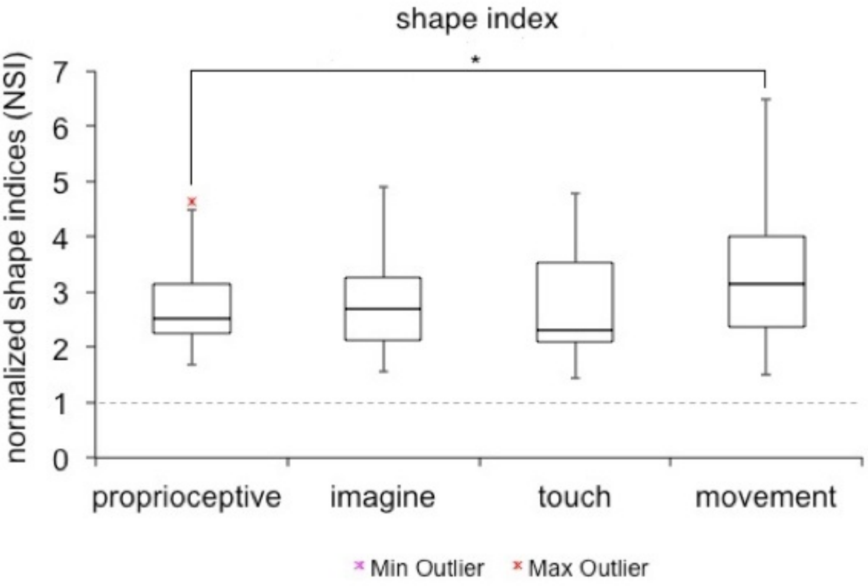

Figure 4. Median normalized shape indices (i.e., overall hand shape) for the conditions proprioceptive, imagine, touch, movement. Top line indicates a significant difference between the proprioceptive and the movement condition. Dotted line indicates a veridical shape of hand. Whiskers represent the data range; minimum and maximum. The x symbols indicate extreme outliers (>1.5 * the inter quartile range (IQR)).

Observational data

All participants were asked in which condition (i.e., when the hand was just lying there, when the finger was touched, when they could move their finger, or when the hand was not there) it was easiest and in which hardest to indicate the landmark on the monitor. The results are given in Table 2.

Table 2. *Participants' response to the question which condition was the easiest/hardest to click to indicate the visually presented landmark.*

	proprioceptive	imagine	touch	movement
easiest	3	1	9	10
hardest	1	20	2	0

Twenty participants were asked how they perceived the shape of their hand underneath the monitor. Twelve participants reported that the hand felt bigger, two of them only felt this in the imagine condition. Four participants even specified it further and perceived the length of their hand felt shortened, and that the width of the hand felt broadened. Two participants reported that they only perceived a broadened width, one participant reported that the thumb felt broadened and the middle finger longer. Another participant reported that the hand felt as its actual size.

DISCUSSION

Since the degree of distortions of the perceived hand representation appears to depend on the sensory information available, our aim was to test whether the perceived hand representation can be differentially modulated. We examined the sensory contributions of different afferent signals (i.e., proprioception, touch, movement) to the implicit hand representation. We replicated previous reports of hand distortions, i.e., width overestimations and length underestimations (Longo & Haggard 2010, Longo et al., 2012; Longo et al., 2015; Saulton et al., 2015; Saulton et al., 2016, Coelho et al., 2016). Similarly, the overall aspect ratio reported here concurs with previous findings as well (Saulton et al., 2015), and indicated that participants perceived their hand as being wider than it is long. Verbal reports indicated that most participants perceived their hand being of different size (mostly bigger) than its actual size.

Debriefing revealed that most participants reported extra sensory information (i.e., touch, movement) to make indicating the landmarks easier, whereas the absence of sensory input (i.e., imagine condition) made the task harder (see below). Intriguingly, the quantitative analyses revealed that the overall shape (i.e., distortion of the hand) actually appears to be fairly robust under varying sensory input circumstances, even when no (informative) sensory information was available (i.e., proprioceptive, touch and imagine condition). However, when participants moved their finger, the perceived distortions became slightly more apparent. A possible interpretation of the latter finding is that the distorted cortical representation might have been updated or more pronounced during the movement condition. During the other conditions the hand was lying still, either below the monitor (i.e., touch, and movement condition) or on participants lap (i.e., imagine condition). One possibility is that over time proprioceptive input was reduced which might have attenuated the true distortions of the perceptual homunculus (Penfield, 1970). Taylor-Clarke et al., (2004) claimed that *if* the distortions in the hand would follow the pattern of the perceptual homunculus, the distortions should be more pronounced than reported in the literature (including the present study), which means that at some level other (i.e., visual) information or experience helps to correct for the distortions originating from the organization of our tactile system. When the finger moved in the movement condition this might have led to renewed (and distorted) sensory input from the hand, and thereby to an increase in the distortion of the perceived hand's representation. Another possibility is that sensory signals (touch (of table), proprioception and movement) compete. As a result, different representations might be in conflict with each other, and therefore the observed larger distortions were the consequence from this conflict. Although methodologically challenging, it would be interesting to investigate the true motor hand representation as it would confirm or rule out the 'conflict theory', that is, to isolate the movement from all the other sensory signals. Also, we used one single movement, and this already slightly distorted the perceived hand representation. It would be interesting to test whether the perceived representations of the hands are even more distorted when fingers are continuously moving.

For the length of the fingers we found that in the touch condition participants were relatively more accurate. This makes sense, since we stroked the participants' finger in the longitudinal direction, and not in the transverse direction. This means that participants received tactile feedback about their finger length, and as a consequence became more accurate overall in the touch condition. Interestingly, the ring finger was most underestimated, and this finding was robust in all sensory conditions. This 'ring finger underestimation' is also shown in Ganea and Longo's (2017) recent work. One way to interpret these findings is by looking at what makes the ring finger different to the other fingers in terms of anatomy and functionality. Anatomically, the ring finger actually differs from all other fingers, since the dorsal side of *only* the ring finger, as opposed to the other fingers, is supplied by two nerve innervations; the median nerve and the dorsal cutaneous branch of the ulnar nerve (Laroy et al., 1998). However, functionally no appreciable differences were reported in the literature with respect to tactile sensitivity (i.e., tactile acuity, pressure sensitivity, point localization; Weinstein, 1968). It has to be noted that only the pads of the distal phalanges of the fingers were tested and not the tactile sensitivity of the whole finger. It therefore remains to be determined whether the difference in peripheral innervation of the ring finger has any consequences for basic somatosensory perception, which may influence higher order representations of the hands (i.e., length judgments).

Perhaps the most intriguing finding is that there was no difference between the proprioceptive and imagine conditions. To recall, in order to generate a representation of a hand (i.e., metrics such as the length of a finger) Longo proposed a model that claims that immediate afferent signals are linked to stored representations of the body, the so-called body model (Longo et al., 2010). Our results however might imply that we do not need *immediate* sensory signals to generate a representation of our hand (and thus have access to the same body model) by merely imagining it. It has to be noted though that afferent input is present in our case (e.g., on the lap), but not immediately below the monitor. Interestingly, recent work of Ganea and Longo (2017) found also similar distortions between the proprioceptive and imagined conditions. The authors conclude that both conditions rely on a stored model of the body that entails its metric features. They further state that this 'proprioceptive imagery' might be important for action planning and whether one is able to perform that action, i.e., take the size of the object and hand (length hand and space between fingers) into account. Ganea and Longo further argue that many of these ideas have been obtained from visual imagery (Kosslyn et al., 2001; Kosslyn et al., 2006), but also other senses, albeit to a lesser extent (Zatorre et al., 1996; Schmidt et al., 2014). These findings all boil down to the notion that merely imagining an action or perception prompt the same mental and even neural representations as the actual action and perception (Pearson, Naselaris, Homles, & Kosslyn, 2015; Albers, Kok, Toni, Dijkerman, & de Lange, 2013). Future research should link reaching or grasping behavior with the proprioceptive representation of the hand or proprioceptive imagery to first test whether proprioceptive maps are used as input for these grasp or reach behaviors, and secondly whether merely imagining it leads to the same results.

Going one step further, our findings, together with those from Stone et al., (2018) and Ganea et al., (2017) suggest that we have access to the same body model by mere imagination. Does this also suggest that lack of sensory afferents not necessarily disrupts the body model? If so, then patients with diminished sensory afferents might still be able to generate body metrics (i.e., shape and size of the body). Unilateral loss of afferent signals (e.g., diminished motor and sensory input) is a frequent and mostly chronic complaint after stroke (Winward et al., 1998; Connell et al., 2008). In this group however, not only afferent signals are affected but the body model itself might also be affected, since the stroke both targets afferent signals and the brain (i.e., body model) itself. It would therefore be particularly interesting to investigate this in a clinical group suffering from peripheral neuropathy. In this disorder *only* the peripheral nerves (e.g., motor and/or sensory nerves) are impaired after a wide variety of etiologies (e.g., vitamin deficiencies, metabolic and/or endocrine deficiencies (Gilron et al., 2015)). Our findings might imply that these patients would still have access to the body model and thus can generate the (distorted) body metrics. Support for this idea comes from a case of Longo and colleagues in 2012, the authors tested a patient with a phantom limb[3] on the body localization task and found similar results between the healthy hand and the phantom hand. In contrast, local anesthetics in the thumb led to an increased (60 to 70%) perceived thumb size in healthy individuals (Gandevia and Phegan, 1999), implying that in this study changes in sensory signals changed the perceived shape of a body part. Interestingly, by using MRI and EEG, Rossini and colleagues (1994) found that an anesthetic block induced immediate, but transient plastic changes of the finger representation at multiple levels of the somatosensory cortex in all tested individuals, which could affect perceived shape (although this was not tested in this particular study). All in all, our findings in healthy individuals indicate that we can always rely on a stored body model, even when imagining our hand. Findings reported in patient studies however imply that after damage, either peripheral or central, changes can emerge in perceived body shape. It would therefore be interesting to systematically investigate whether body metrics change as a function of diminished sensory or motor signals after both peripheral and central damage. These findings in clinical groups might have implications for what we currently know about perceived hand representations.

Finally, verbal reports indicated that almost all participants reported the touch and movement condition to be the easiest in generating a representation of the hand, whereas the

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[3] One might argue that amputation suggests both a peripheral change (i.e., phantom limb) and a central change (i.e., reorganization in the brain), which often has been described after phantom limb pain (Flor et al. 1995; Harris 1999; Devor 2013; Flor et al. 2006).

hand representation was actually slightly more distorted at least for the movement condition. We suggest that participants felt perhaps more confident in performing the task after receiving extra sensory information from multiple sources (i.e., proprioception *plus* movement or touch). Interestingly, participants most of the time reported that the hand felt wider or bigger, even when they knew it was smaller. These findings also suggest that explicit accounts of this task are inaccurate or at least differ from what the task is measuring: an implicit representation of the hand, a distinction that was also made by Longo and Haggard (2012).

In conclusion, in this study we confirmed the characteristic distortions of hand shape: an overestimation of width and underestimation of length, reflecting the anisotropies in somatosensation "greater tactile acuity signals on the hand dorsum mediolaterally than proximo-distally". The magnitude of distortions depends partly on the sensory information available (i.e., different representation in width with movement and different representation in length with touch). The overall shape seemed robust across conditions, which might imply that the implicit representation of our body relies on a stored body-model, which is unaffected by different sensory input. Therefore it would be of interest to investigate whether body metrics change as a function of diminished sensory or motor signals after both peripheral and central damage. These findings in clinical groups might have implications for what we currently know about perceived hand representations.

Chapter 6

Hand representation in patients with somatosensory deficits after right hemispheric stroke

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ABSTRACT

Research shows that the somatosensory system plays an important role in body representation (BR). The current study aims to examine the effect of long-term somatosensory loss in the hand on the metric features of the BR, by including patients with somatosensory loss due to stroke and healthy age-matched controls. Two types of representations were examined in both hands; a more visual, explicit BR and a more somatosensory, implicit BR for which a template matching tasks (TMT) and a Body localization task were performed respectively (Longo & Haggard, 2012). In total 21 healthy controls and 13 right hemispheric stroke patients were included.The patients were subdivided into groups with mild and severe somatosensory impairments. The results showed that all groups display the classical distortions (i.e., short fingers, and broadened hands) on the body localisation task. A few patients experienced a disproportionally large hand. This finding seems to be linked to diminished body awareness. On the template matching, most patients performed accurately. Surprisingly, patients in the severe group perceived the overall shape as to be longer than it is wide. Overall, patients with somatosensory impairments appear to have access to a multimodal representation of the hand.

INTRODUCTION

Although we often see our own hands, we do not frequently think about their shape or dimensions. We would be fairly accurate in drawing the shape of our hands. However, without vision, we perceive them as highly distorted, featuring broadened hands and shortened fingers (Longo et al., 2010; Saulton et al., 2015) reflecting the anisotropies in somatosensation “greater tactile acuity signals on the hand dorsum mediolaterally than proximo-distally” (Longo and Haggard, 2010, p. 11728). Longo et al., (2010) further suggest that somatosensation in and of itself is unable to provide accurate information about the shape and dimensions and proposes that input from multiple senses must be *integrated* in stored representations of the body. This ‘stored body model’ contains information about the relative shape and dimensions of body parts. Nevertheless, intact somatosensation (such as proprioceptors and joint angles) has been found to be important for perception of body dimensions. There is evidence in healthy individuals that somatosensory signals can influence the metric features of body representation. Gandevia and Phegan (1999) found that after inducing local anesthetics to the thumb its perceived size increased by 60-70 percent. This also fits into the experience of a larger mouth and lips after dental anesthesia. Likewise, Longo, Kammers, Gomi, Tsakiris, & Haggard (2009) found that modulating proprioceptive input changes the perceived midline of an arm. By vibrating the muscle tendon, these researchers induced proprioceptive conflict in the arms of healthy individuals resulting in a perceived shift towards their elbow. On a slightly different note, patients suffering from complex regional pain syndrome, which involved shrinkage of the primary somatosensory cortex, perceived their affected limb as larger than it actually was. Even the magnitude of distortions can be modulated, while the overall shape (e.g., broadened hand and shortened fingers) was still preserved (Longo, 2015). For instance, Longo (2015) found that when fingers are spread, instead of holding them together, the perceived hand width is increased, indicating that proprioceptive changes can modulate the degree of distortions as well. The idea that somatosensory input is important for perception of body dimensions, is particularly interesting for certain groups that have diminished somatosensation. In other words, we could argue that patients with somatosensory loss may perceive their hand different than healthy individuals do. Therefore, the goal of the current study is to investigate the effect of chronic somatosensory loss in the affected hand, due to stroke, on the representation of our body (i.e., metric features such as shape and dimensions).

The aforementioned studies support the idea that current somatosensory input is important for perception of body part dimensions. On the contrary, recent findings from our lab (Stone, Keizer, Dijkerman, 2018; Smit, van der Smagt, van der Ham, Dijkerman, under review) and also other labs (Ganea and Longo, 2017) suggest that we can also have access to stored knowledge of our body by mere imagination. This might imply, although not directly tested in these studies, that a lack of afferent sensory input does not necessarily disrupt the body size perception. If this is the case, stroke patients with diminished sensory input, which is common after stroke (Winward et al., 1998; Connell et al., 2008), might still be able to perceive bodily dimensions in a similar way to healthy individuals. However, not only afferent signals can be disturbed by the stroke, but the stored representations of the body dimension (e.g., body model) itself might also be affected regardless of diminished sensory input. For instance, epilepsy and migraine can result in micro- or macrosomatognosia (Weijers, Rietveld, Meijer, & de Leeuw, 2013), while somatosensation is usually intact in these individuals. In micro- and macrosomatognosia body parts (or the entire body) are perceived as abnormally large or small, respectively (Podoll, & Robinson, 2000). Likewise, tactile distance perception in patients with anorexia nervosa seems to be modulated by these stored representations, that is, these patients are likely to overestimate tactile distances on the skin (Keizer et al., 2011, Keizer et al., 2012, Spitoni et al., 2015).

While previous studies suggest that disturbances in body part size perception can occur following changes in afferent somatosensory input and centrally stored body models, so far it has not been investigated to what extent patients with somatosensory deficits following stroke perceive the size of their hands differently. The current study aims to investigate the effect of chronic somatosensory loss in the hand, due to stroke, on the representation of our hands (i.e., metric features such as shape and dimensions). Two types of metric representations will be examined in both hands; a more visual, explicit representation (Longo and Haggard, 2012) and a more somatosensory, implicit representation (Saulton, Dodds, Bülthoff, & de la Rosa, 2015; Longo and Haggard, 2010). With respect to the latter, an implicit hand size perception task called the body localization task will be administered (adapted version of Longo, 2010). As mentioned above, both loss of afferent input and damage to the stored body model might affect perception of hand size. However, the imagery study (Longo & Haggard, 2012) suggest that afferent input is not necessary. If loss of afferent input influences hand size perception, then we expect an enlarged hand. However, if we have conscious knowledge about our body which seems unrelated to afferent input, we would find similar results to that of healthy controls. Additionally, an explicit representation that is based on visual input about the hand will be tested with a template (i.e., hand) matching task (adapted version of Longo and Haggard, 2012). According to Longo and colleagues (2015, 2017), both the explicit and implicit body models lie on opposite ends of the same continuum, and rely on different sensory afferents. Somatosensation seems important in the implicit body model, and visual information more dominant in the explicit body model. The latter representing a near veridical representation of the body. The visual modality in our stroke patients is usually spared (damage to the middle cerebral artery and not the posterior artery), therefore we anticipate that their conscious representation of the hand will be near veridical, similar to that of controls.

METHODS

Healthy control and Patient recruitment and selection

In total 27 healthy controls (11 females) and 13 patients (5 female) were included in this study, see Table 1 for demographic information, Table 2 for patient details and Table 3 for patient observations. Originally, 15 patients participated, but two patients were excluded, resulting in 13 patients in total; one patient was excluded due to severe problems in language expression and reception, the second patient suffered from Wallenberg syndrome and this patient displayed bilateral sensory problems which is a reason for exclusion for this study.

Table 1. *Demographic information patients and healthy controls. Average age (sd), gender, lesion site and average laterality quotients (sd).*

Group	n	Age	Gender (F/M)	Lesion Site**	Laterality quotient***
Control total	27	52.91 (6.76)	11 F	n.a.	85.9 (40.51)
Patient total	13*	60.07 (15.87)	5 F	MCA-r	80.32 (31.43)

*Patient K was excluded, in total 15 patients were tested ** n.a. = not applicable; MCA-r = Middle Cerebral Artery right, The Edinburgh Inventory (Oldfield, 1971): Left-handed between −1 and −100 (extreme left-handed between -80 and -100); Right-handed between 1 and 100 (extreme right-handed between 80 and 100); Mixed handed between −79 and 79.

Healthy controls (hereafter HC) were recruited through online advertisements and were screened (by questionnaire) to ensure inclusion and exclusion criteria. HC were included when they displayed (1) no somatosensory problems, (2) no motor problems, (3) no neurological problems and (4) had no history of substance abuse or psychiatric disorders.

Patients (PT) were recruited from the stroke database at University Medical Centre Utrecht (UMCU) and were included when they suffered somatosensory and/or proprioceptive and/or motor problems (typically following an infarct in the right middle cerebral artery (MCA-r)). PT had to be in a chronic stage, which is over 4 months' post stroke (Nijboer, Kollen & Kwakkel, 2013). Patients completed a screening questionnaire about their somatosensory and motor problems.

Both groups were screened prior to the experimental tasks. This screening consisted of (1) a neglect screening using the Star Cancellation task (cut-off ≤ 44) (Friedman, 1992) of the behavioural inattention test (BIT) (Wilson, Cockburn, & Halligan, 1987), (2) a proprioception task for both thumbs (cut-off ≥ 1 error) (Gilman, 2002), (3) The Comb and Razor Test to test for personal neglect (cut-off -0.06 - 0.04) (McIntosh, Brodie, Beschin, & Robertson, 2000), (4) a visual extinction task (cut-off < 15), (5) the Stroke Upper Limb Capacity Scale (SULCS) (cut-off score < 10) (Houwink, Roorda, Smits, Molenaar & Geurts, 2011) and at last (6) the two point discrimination task to assess for somatosensory deficits (cut-off score for the index finger of > 2 errors). In total 2 HC's were excluded because they did not pass the screening tests. One participant did not understand all test instructions, and another participant scored below cut-off on the two-point discrimination task.

Prior to initiation of the experimental tasks, patients received a short interview about their symptoms (summarized in supplementary Table A1), followed by the screening tasks (for the screening scores see Table 3). Most patients scored below cut-off on either the proprioception task, the Stroke Upper Limb Capacity Scale (SULCS) and/or the two-point discrimination task. One patient (PT D) scored below cut-off on the Star Cancellation. However, the errors were not lateralized. Another patient (PT A) scored below cut-off on the visual extinction task and the comb and razor test. The patient was able to look at unilateral visual stimuli, but showed extinction when bilateral stimuli were presented. The score on the Star Cancellation was however above cut-off. Based on the latter task, where she showed she could evenly distribute attention across a field with targets, we included her. We observed her behaviour during the experimental procedure.

Table 2. *Details from screening interview highlighting their most prominent (sensory) complaints.*

PT	Details from interview
A	Cannot move left hand. "When sitting in the car next to my husband I sometimes experience his arm as mine". Reduced awareness of somatosensory problems.
B	Unable to control certain movements in left hand; sometimes the impaired hand does not move, or the impaired hand makes a different move.
C	Somatosensory functioning in left hand improved over time. Spouse thinks that patient's left hand still lies in a certain atypical way.
D	Somatosensory problems in his left arm/elbow not in his fingers; still plays the guitar. Unable to control certain movements, clumsy; bumps into objects and people.
E	Feeling of loss of (location) left arm; difficulty in discriminating between temperatures (burns himself while cooking cooking); sometimes hostile thoughts towards his left arm and leg.
F	Feeling of touch is reduced in left hand, arm, and feet; feels like left leg is not part of the body; problems in fine motor skills.
G	Feeling of touch is reduced in left arm/leg (also right leg); only feels pain in left arm; less feeling of touch in right leg; more difficulty with localization of touch; difficulty in naming limbs due to aphasia; has the feeling her left arm is not hers (but of her husband); Also problems in size: "a fly on my arm feels like an elephant".
H	In the acute stage there was a reduction in feeling of touch in the left limbs. Complaints dissipated over time.
I	In the acute stage there was a reduction in feeling of touch in the left limbs. Complaints dissipated over time.
J	Feeling of touch is reduced; difficulty in localization of touch; 'forgets' arm; negative cognitive feelings; arms feels bigger and heavier than it is; skin feels extremely cold.
L	Feeling of touch is reduced; experiences a constant numb, tingling, sensation in left hand; reports paraesthesia's such as hold and cold pain in limbs; reports an upper-left visual field defect
M	Feeling of touch is reduced in left hand and left cheek, these complaints worsen throughout the day; fingertips feel numb and cold, sometimes he experiences tingling sensations; when grabbing an object, watching his own movements is necessary; sometimes his left arm moves involuntarily; his left arm/hand feels heavier inside and colder outside; cannot estimate temperature properly; has the feeling that his left hand is not part of the rest of his body, "it is there but not useful".
N	Does not think that the feeling of touch is less; all of the left arm somatosensory and motor problems disappeared in the subacute stage. Apart from some concentration problems pt. is functioning fine and has no other complaints.

Table 3. *Mean (M) and Standard Deviation (SD) of the scores on the screening-tests for the left hand (LH) and right hand (RH) administered in patients and controls: C&R, VE, SC are screening for neglect, Proprioception, 2PD and von Frey = somatosensory screening, SULCS = screening motor abilities. Controls did not perform the von Frey. Average scores are indicated in bold. Individual scores of the patients are given below (patient A – J). Patients whom scored below cut – off are indicated in blue. Patient K was excluded from this study due to cognitive problems and is therefore missing in this table.*

Tests[1]	C&R (CU<-0.5)		VE (CU<15)		SC (CU≤51)		Proprioception (CU>0)				2PD (CU>0)				Von Frey (CU>3)				SULCS (CU<4)	
	M	SD	M	SD	M	SD	M LH	SD LH	M RH	SD RH	M LH	SD LH	M RH	SD RH	M LH	SD LH	M RH	SD RH	M	SD
controls	**0.0**	**(0.1)**	**14.8**	**(0.9)**	**51.6**	**(9.7)**	**0.0**	**0.0**	**0.0**	**0.0**	**0.3**	**0.7**	**0.5**	**1.0**					**10**	**0.0**
patients	**-0.09**	**(0.37)**	**13.79**	**(2.46)**	**53.3**	**(1.1)**	**2.5**	**4.3**	**0.36**	**1.3**	**3.8**	**3.0**	**1.7**	**2.2**	**4.51**	**1.70**	**3.73**	**0.43**	**7.6**	**3.8**
patient A	-0.14		10		52		5		0		3		2		3.84		2.44		1	
patient B	-0.04		15		54		0		0		0		3		2.44		2.83		10	
patient C	0.71		15		53		0		0		6		0		2.44		3.03		10	
patient D	-0.11		15		51		0		0		2		2		3.22		3.03		10	
patient E	-0.22		15		54		10		0		7		0		>6.65		2.44		1	
patient F	0.00		15		54		0		0		7		0		2.40		2.44		10	
patient G	-1.00		15		54		10		0		8		0		>6.65		2.83		5	
patient H	-0.05		15		54		0		0		1		2		2.44		2.40		10	
patient I	0.04		15		54		0		0		0		0		1.65		1.65		10	
patient J	-0.51		12		54		10		0		8		0		4.31		2.44		1	
patient L	0.05		7		51		0		0		5		6		3.03		3.22		9	
patient M	0.11		15		54		0		0		3		3		4.08		3.61		10	
patient N	-0.08		15		54		0		0		1		0		3.61		3.84		10	

[1] Tests: C&R = Comb and Razor; VE= Visual Extinction; SC = Star Cancellation; 2PD= 2point discrimination; SULCS = Stroke Upper Limb Capacity Scale. [2] CU= Cut-Off

Study design and general procedure

Eleven patients were seen once. Two patients in the patient group were seen twice in order to avoid feelings of tiredness. All HC were seen once. Both patients and HC started with signing the informed consent, followed by the screening for sensorimotor functions. Thereafter, both groups started with the experimental tasks. Experimental tasks were counterbalanced (see Figure 1).

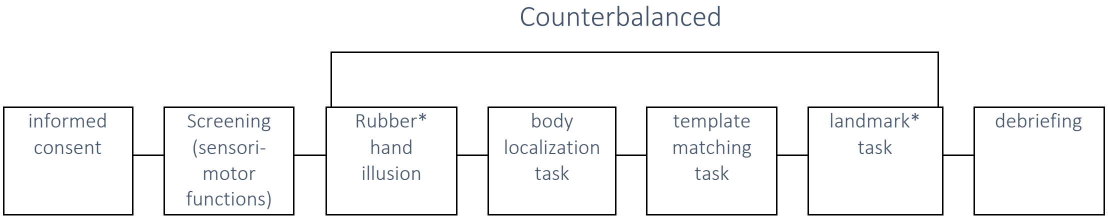

Figure 1. Timeline of experimental tasks.
* Not analysed in this study

A questionnaire was filled out to check whether participants met the inclusion criteria. If so, a date was set to perform the experiments at the Utrecht University. Prior to the experimental task, written informed consent was given, and additional questions were addressed. When testing a patient, usually the spouse was also present. The informed consent and the screening were conducted in a patient friendly room. The experimental tasks were conducted in a lab with no distractors. In order to avoid sequence effects, experimental tasks were counterbalanced. Both PT and HC were allowed to have a break when needed. The tasks duration was approximately 120 - 130 minutes. In the next section we provide a detailed procedure and stimuli for the experimental tasks: the body localization task, the template matching task and the rubber hand illusion. After performing all the experiments, the experimenter debriefed the participants.

Task, procedure and stimuli

Body localization task

An adapted version of the body localisation test was used (based on the task of Longo and Haggard (2010)). The participants were seated in a dimly lit room. The task consisted of 2 conditions, a left-hand condition and a right-hand condition for both the control group and the clinical group. In total there were 10 landmarks; all 5 knuckles and all 5 fingertips (e.g., centre of the nail). These landmarks were marked with small dots (Figure 2). Participants first had a practice round where they had to point at the landmark that the experimenter requested in random order (30 seconds in total). Thereafter, the hand was placed underneath a horizontally tilted square computer screen (40 by 40 cm) that was placed on a stand (15 cm in height). The hand was positioned with the nail of the middle finger 5 cm from the top of the monitor. After 10 practice trials, the participants were instructed to click to indicate the felt position of the landmark that was presented on the screen. This landmark was presented (one at a time) in text (e.g., “knuckle ring finger”) at the top of the screen in random order. In order to prevent feedback of a previous mouse-click, the cursor jumped after each click to a random y-coordinate at the right side of the screen. Each landmark (10 in total) was tested 10 times in random order, resulting in a total of 100 trials per condition. The duration of the task was 30 minutes. The first outcome measure was the percentage of misestimation for the width of the hand and for the length of the hand separately. The second outcome measure, called the shape index, reflects the overall aspect ratio of the hand, which takes both length and width into account (see data analyses for more details).

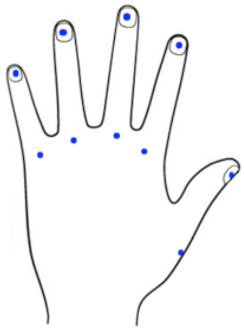

Figure 2. Left hand with the 10 landmarks (blue). Landmarks are based on the landmarks used in Longo and Haggard (2010).

Template matching task

In the template matching task (also based on Longo & Haggard, 2010) we measured the explicit body representation. The task consisted of four conditions: Left hand length, left hand width, right hand length and right hand width. Prior to the task, a picture of the right hand and a picture from the left hand were taken. The pictures were taken in front of a green screen, 150 cm in front of the participant and immediately uploaded in MATLAB. In a custom script the pictures were either stretched or compressed in length or width (depending on which condition) by 5- 35% in steps of 5%, producing a series of a total of 15 images. Values of the images were between 0.65, indicating 65% of the actual width or length, and a maximum stretch of 1.35. Images with the value 1 indicate the actual width or length of the participant's hand. Participants sat in front of a computer and were shown the produced images. Depending on the condition, participants had to click to indicate whether the hand on the picture was either longer or shorter, or wider or slender than their own hand. In order to prevent comparing the visual on screen image to their own hand, participants were unable to see their hands during the experiment. The procedure of shown images was staircased. For each condition, staircases could either start with an image that was 75% of the length/width or start with an image that was 125% of the length/width. For the staircase a one-up-one-down procedure was used, with initial step sizes of 5% that decreased after each reversal by 3%, 2% or 1% and the task terminated after 13 reversals. The number of trials ranged from 13 to 80. Averages of the last 5 reversals (number between 0.65 and 1.35) for both staircases were calculated and reflect the perceived threshold for length or width threshold. The primary outcome measures were the % misestimations for both length and width and the shape indices of the hand's overall shape.

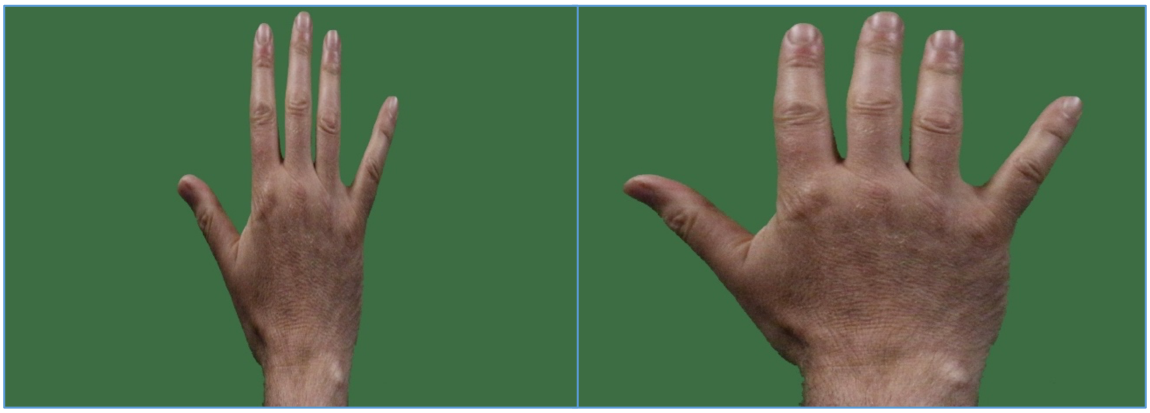

Figure 3. Images ranged between 65% (left panel) of the actual width or length and a maximum stretch of 135% (right panel). Images with the value 1 indicate the actual width or length of the participant's hand.

DATA ANALYSES

Analyses body localisation task

The Body localisation task had 2 outcome measures: *Percentage of misestimation:* the perceived dimensions of a finger were based on (the clicked) x and y coordinates. For the length this was the distance between fingertip and the knuckle at the base of that particular finger, and for the width this was the distance the knuckle of the little finger and the knuckle of the index finger (similar to Longo et al., 2010; Saulton et al., 2015, 2016). In order to calculate the distance between the x-y coordinates from tip to x-y coordinates of the knuckle, the following (Pythagorean) equation was used:

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y)^2}$$

Once the displacement was calculated for each body part, the value was converted into mm. One pixel at the screen was .38 millimeters (mm). Then the percentage misestimation with respect to the actual size was calculated:

$$\textit{percentage of misestimation} = \frac{perceived\ size - actual\ size}{actual\ size}\ x\ 100$$

A positive value indicates an overestimation of the length or width with respect to its actual size; a negative value indicates an underestimation.

Shape index: this reflects the overall shape of the hand and takes both length and width into account. The shape index was calculated for the actual and the perceived hand:

$$shape\ index\ (SI) = \frac{width\ hand}{length\ (middle\ finger)}\ x\ 100$$

For interpretation convenience and comparison across tasks and with previous studies where they use different body parts (Stone et al., 2018), we normalized the shape index with the following formula:

$$normalized\ SI\ (NSI) = \frac{perceived\ SI}{actual\ SI}$$

A NSI of 1 indicates a veridical shape of the hand. A NSI above 1 indicates that participants perceived their hand to be wider than it is long, and when it is below 1, participants perceived their hand to be longer than it is wide.

Analyses Template Matching Task

The TMT had outcome measures similar to those for the body localisation task (i.e., percentage misestimations and shape indices).

To recall, the last five reversals per condition were averaged, which resulted in 4 averages per hand, the width (125% start staircase), width (75% start staircase), length (125% start staircase) and length (75% start staircase). Thereafter we averaged the different staircases of the width, resulting in a percentage of the misestimation for the width of the hand and we averaged the different staircases of the length, resulting in a percentage of the misestimation for the length of the hand. The next step was to multiply the misestimation of the width of the hand with the actual measured width of the hand, to determine the perceived width size. The same was done for the length and for both hands. Thereafter, the shape indices and the normalized shape indices were calculated.

RESULTS

On the basis of the screening results (see Table 3 of each individuals' performance) we divided our patients in two groups: A severe group and a moderate group. Patient A, E, G and J scored below cut-off in all screening tests (i.e., 3 tests on somatosensory and 1 test on motor functioning) and belong to the severe group (hereafter PT severe). Patient C, D, F, H, L, M, N scored below cut-off on at least one, but not all, somatosensory screening tests and belong to the moderately impaired group (hereafter PT moderate). Patient B and I are excluded from group analyses because no somatosensory or motor problems were present during the screening procedure, however their individual results can be found in Supplementary Material B. In Supplementary Material B we present all cases individually and tested their scores to that of healthy controls, using Crawford statistics (Crawford & Garthwaite, 2002).

In the current result section, we statistically compared the two patient groups to healthy controls first on the body localization task, second the template matching task, and third the rubber hand illusion. Next to quantitative data, we provide a table with observations during screening and testing. We conclude the result section with a summary of results.

For readers' convenience, we attempted to provide structure throughout the results section by using bold font when analyses revealed (near) significant differences. For reasons of consistency we only used non-parametric tests and therefore medians were displayed in Figures. Friedman repeated measures were used testing multiple within subject variables. Wilcoxon signed rank test was applied to test within-subject effects (left vs. right hand) and the Kruskal-Wallis for between group effects (severe, moderate, HC).

Alpha levels of .05 (two-tailed) were used for the statistical tests. In a custom MATLAB script boxplots were generated. JASP, JAMOVI and Crawford statistics were used for statistical analyses.

RESULTS BODY LOCALISATION TASK

Percentage misestimation of the width of the left and right hand

Within subject analyses: For all 3 groups (severe, moderate, HC) we analysed the percentage misestimation for the left and right hand. As stated before (data-analyses) Wilcoxon signed rank test was applied to test within-subject effects (left vs. right hand) and the Kruskal-Wallis for between group effects (severe, moderate, HC).

As can be seen in Figure 4, for the percentage misestimation of width of the hand, analyses revealed no differences between the left and right hand in all groups, for PT severe, $Z=-0.54$, $p= .75$, PT moderate: $Z= -0.56$, $p= .64$, and HC: $Z=-0.49$, $p= .64$.

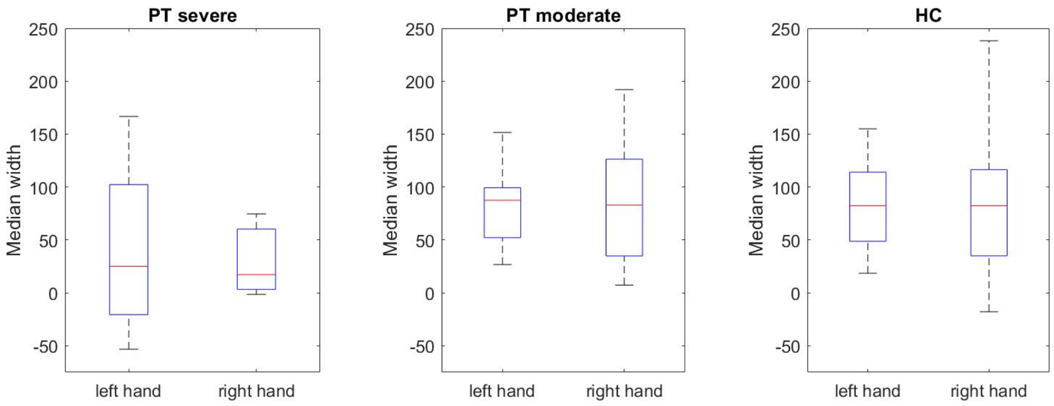

Figure 4. Median percentage mis-estimations for the left and right width of the hand in patients (PT) in the severe and moderate group and healthy controls (HC). Whiskers represent the data range; minimum and maximum.

Between subject analyses: Analyses for the left hand revealed no differences between the three groups, *H*(2)= 1.73*, p*= .421, ε^2.0444, nor any differences between groups for the right hand, *H*(2)= 3.24*, p*= .198, ε^2.0853.

Percentage mis-estimation of the length of the left and right hand

Within subject analyses: For the severe group (see Figure 5) analyses revealed no differences between the left and right hand for each finger, little finger: Z=0.00, *p*= 1.00, ring finger: *Z*= 0.00, *p*= .1.00, middle finger: *Z*= 1.07, *p*= .500, index finger: *Z*= 0.54, *p*= .75 and thumb: *Z*= -1.07, *p*= .500. For the moderate group, analyses revealed no differences between the left and right hand for little finger: *Z*= 0.98, *p*= .3 75, ring finger: *Z*= 0.56, *p*= .64, nor the middle finger: Z= -0.84, *p* = .46. **Analyses revealed a significant difference between hands for the index finger: Z= -2.10, *p*= .04 and a significant difference for the thumb Z=-2.52, *p*= .008, indicating the underestimation of index finger and the thumb was less pronounced for the right hand**

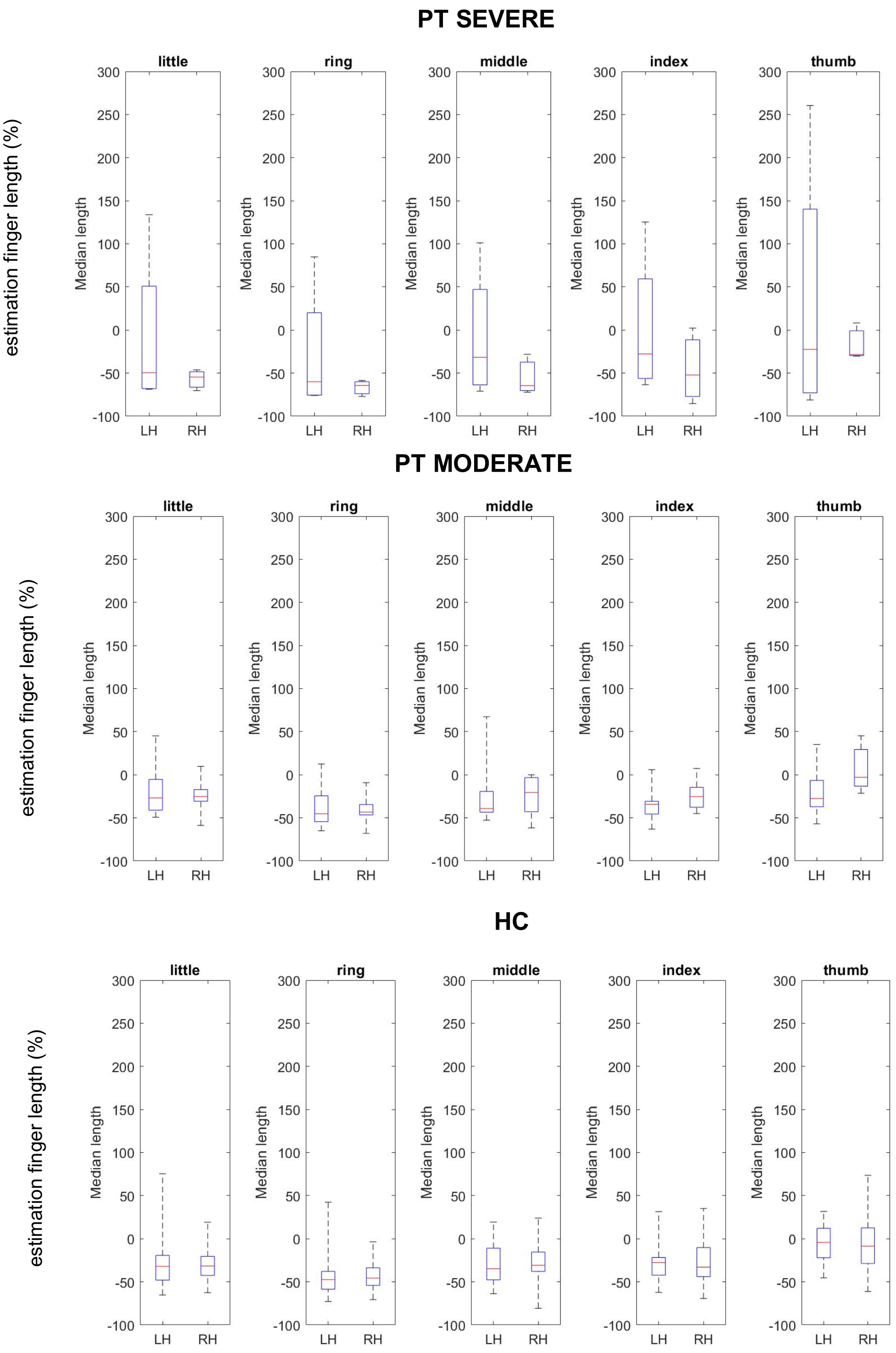

Figure 5. Median percentage mis-estimations in all groups (PT severe; PT moderate; HC) for the length of the little finger, the ring finger, the middle finger, the index finger and the thumb. Each plot displays the left hand (LH) and the right hand (RH). Whiskers represent the data range; minimum and maximum.

For the control group (see Figure 5) analyses revealed no differences between the left and right hand for each finger, little finger: *Z= -1.14*, *p*= .26, ring finger: *Z*= -1.18, *p*= .24, middle finger: *Z*= -1.57, *p*= .12, index finger: *Z*= -0.23, *p*= .83 and thumb: *Z*= 0.52, *p* = .61.

Between subject analyses: None of the fingers of the left hand differed between the three groups (little: *H*(2)= 1.5322*, p*= .465, ε^2= .03929*,* ring: *H*(2)= 1.1703*, p*= .557, ε^2= .03001*,* middle: *H*(2)= 0.0231*, p*= .989, ε^2= 5.91e-4, index: *H*(2)= 0.3471*, p*= .841, ε^2= .00890, thumb: *H*(2)= 1.4808*, p*= .477, ε^2= .03797*.* **Results were slightly different for the right hand, analyses revealed differences between the three groups for the little finger and the ring finger (little: *H*(2)= 6.46*, p*= .04, ε^2= .17004*,* ring: *H*(2)= 5.61*, p*= .06, ε^2= .14765) and not the other fingers** *(*middle: *H*(2)= 3.78*, p*= .151, ε^2= .09957, index: *H*(2)= 1.62*, p*= .446, ε^2= .04251, thumb: *H*(2)= 2.57*, p*= .277, ε^2= .06756). **Post-hoc, Bonferroni corrected, pairwise comparisons revealed a difference between only the severe and moderate group for the little finger, *W*= 3.06*, p*= .033 and a trend for the ring finger, *W*= 3.15*, p*= .062. These results indicate that the underestimation of these two fingers was more severe for the severe group relative to the moderate group.**

Normalized shape indices

Within subject analyses: As can be seen in Figure 6, for the shape indices, analyses revealed no differences between the left and right hand in all groups, for PT severe, *Z*= 0.00, *p*= 1.00, PT moderate: Z= -0.28, *p*= .844, and HC: Z= 0.68, *p*= .51.

Between subject analyses: Analyses for the left hand revealed no differences between the three groups, *H*(2)= 3.104*, p*= .212, ε^2.0796, nor any differences between groups for the right hand, *H*(2)= .983*, p*= .612, ε^2.0259.

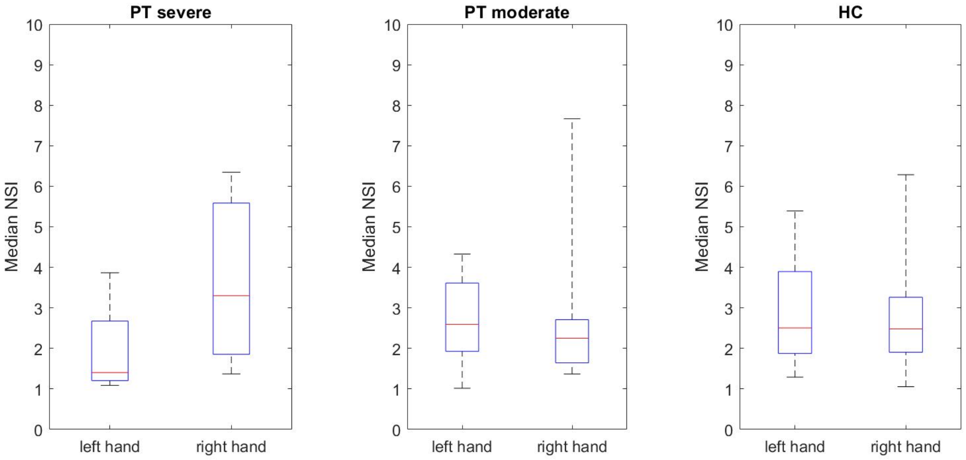

Figure 6. Median normalized shape indices (NSI) for the left and right hand in patients (PT) in the severe and moderate group and healthy controls (HC). A value of 1 indicates a veridical shape of hand. Whiskers represent the data range; minimum and maximum.

Individual analyses

For individual analyses we used Crawford statistics Crawford & Garthwaite, 2002, see supplementary material for an overview of the results. It is important to note that none of the patient data revealed any outliers. All patients were fairly consistent in their localisation decision. We see that compared to HC, patient A^{severe} significantly overestimated the hand width whereas patient J^{severe} significantly underestimated the hand width of their left (affected) hand, and not their right (unaffected) hand.

With respect to the length for the left hand we see that patient A^{severe} and patient F^{moderate} significantly overestimated the length of most fingers as opposed to HC's, whereas other patients underestimated their finger lengths, similar to HC. Interestingly, the length of the thumb was underestimated significantly by PT E^{severe}, J^{severe} and L^{moderate} compared to HC. Patient A^{severe} significantly overestimated the length of the thumb. Most patients, however did not differ from HC's.

With respect to the length for the right hand, patient E^{severe} and patient J^{severe} significantly underestimated their right index finger and middle finger, respectively. Most patients, however did not differ from HC's.

Shape indices only differed for PT J^{severe} and M^{moderate} for the right, healthy, hand. These results indicated that the right hand for these patients was considered more distorted (wider than long) than the right hand of their healthy counterparts.

RESULTS TEMPLATE MATCHING TASK

Percentage mis-estimation of the width of the left and right hand

Within subject analyses: The Wilcoxon signed rank test was applied to test within-subject effects (left vs. right hand) and the Kruskal-Wallis for between group effects (severe, moderate, HC). As can be seen in Figure 7, for the percentage misestimation of the width of the hand, analyses revealed no differences between the left and right hand in all groups, for PT severe, $Z = -1.60$, $p = .18$, PT moderate: $Z = -1.12$, $p = .31$, and HC: $Z = 0.44$, $p = .67$.

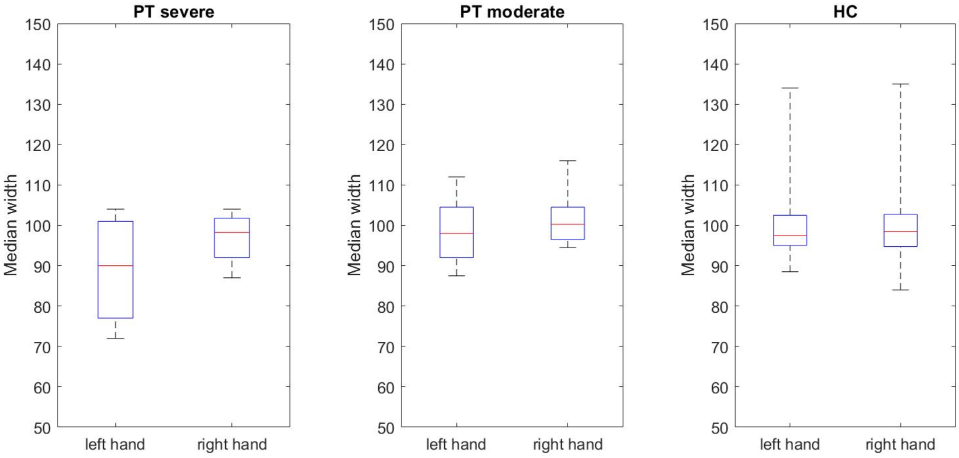

Figure 7. Median percentage mis-estimations for the left and right width of the hand in patients (PT) in the severe and moderate group and healthy controls (HC). Whiskers represent the data range; minimum and maximum.

Between subject analyses: Analyses did not reveal differences between the groups for the left hand, *H*(2)= 1.31*, p*= .519, nor for the right hand, *H*(2)= 1.81*, p*= .404.

Percentage misestimation of the length of the left and right hand

Within subject analyses: For the severe group (see Figure 8) analyses revealed no differences between the left and right hand, *Z*= 0.73, *p* = .63, neither in the moderate group, *Z*= -0.56, *p*= .64, nor in HC: *Z*= -0.87, *p* = .39.

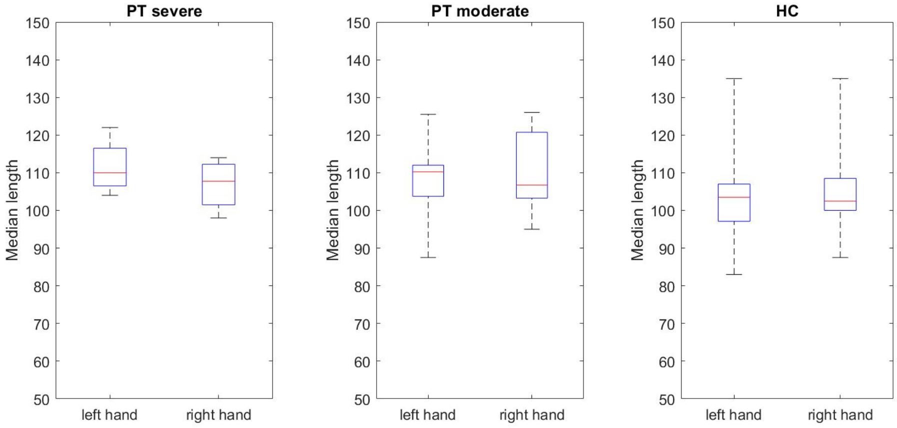

Figure 8. Median percentage mis-estimations for the left and right length of the hand in patients (PT) in the severe and moderate group and healthy controls (HC). Whiskers represent the data range; minimum and maximum.

Between subject analyses: Analyses did not reveal differences between the groups for the left hand, $H(2)$= 3.98, p= .137, nor for the right hand, $H(2)$= 1.40, p= .498.

Shape indices of the left and right hand

Within subject analyses: As can be seen in Figure 9, for the shape indices, analyses revealed no differences between the left and right hand in all groups, for PT severe, Z= -1.83, p= .13, PT moderate: Z= -0.42, p= .74, and HC: Z= 0.471, p= .65.

Between subject analyses: Analyses did reveal near significant differences between the groups for the left hand, $H(2)$= 5.298, p= .071. **Post-hoc, Bonferroni corrected, pairwise comparisons revealed a near significant difference between only the severe group and the HC: W= -3.13, p= .071, ε^2= .1431, indicating the overall shape was slightly more distorted for these patients (longer than wide) as opposed to HC.** Analyses revealed no significant differences between groups for the right hand, $H(2)$= 0.699, p=.705, ε^2= .0189.

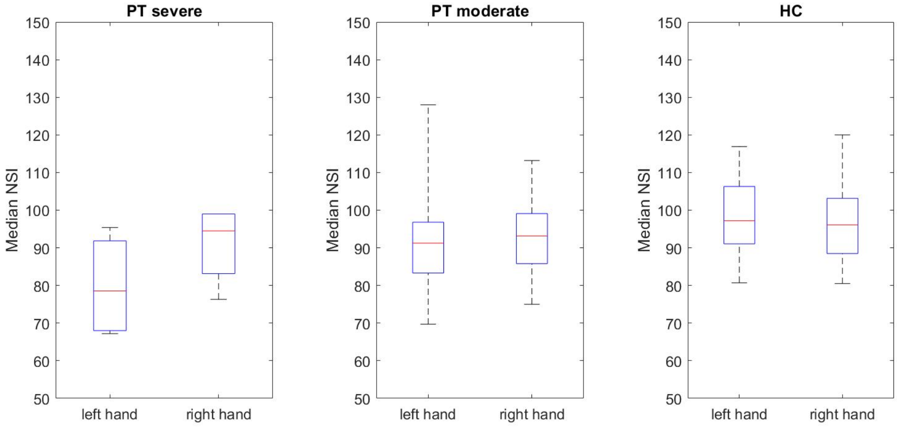

Figure 9. Median normalized shape indices (NSI) for the left and right hand in patients (PT) in the severe and moderate group and healthy controls (HC). A value of 1 indicates a veridical shape of hand. Whiskers represent the data range; minimum and maximum.

Individual analyses

When addressing individual analyses against controls, we see (supplementary material) that PT J^{severe}, opposed to HC, underestimated the width of the left hand. Other patients, however, did not differ from HC's. For the length, PT $H^{moderate}$ overestimated the right hand. Other patients did not differ from HC's.

The overall shape of the left hand did however differ from HC for some patients. Patients A^{severe}, J^{severe}, L^{moderate} differed significantly. PT A^{severe}, J^{severe}, and L^{moderate} estimated their hand longer than it was wide, compared to controls whom estimated their hands nearly veridical. Patient L^{moderate} estimated the left hand wider than long. For the right hand, PT J^{severe} also differed significantly from HC, revealing the same pattern as for the left hand.

Observations during screening and testing

When screening and testing patients, we have noticed that not all behaviour could be quantified. In order to present a complete picture of patients' performance we highlighted important observations in Table 4.

Table 4. *Observations during interview, screening and experiments. Patient B and I were excluded from group analyses, but are found in supplementary data B.*

PT*	Observations
A^{severe}	Screening: Observable problems in somatosensation, temperature discrimination, hostile towards hemiplegic hand (e.g., verbal (calling names) and physical (hitting)); reduced awareness of/and indifference of deficits. Body localisation task: Thought her affected hand was extremely large. Rubber hand illusion task: When affected hand was confronted with rubber hand, pt. could not disentangle the fake hand from her own. Pt. experienced body ownership when fake hand was not in anatomically plausible angle (e.g., 45 degrees).
B^{excluded}	Screening: No observable somatosensory problems, nor with moving both arms/ hands. Patient has a short attention span; eye focus problems. Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
C^{moderate}	Screening: Observable somatosensory problems in left hand; no observable motor problems. Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
D^{moderate}	Screening: No observable somatosensory problems; no problems in moving both arms/hands. Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
E^{severe}	Screening: Observable somatosensory problems; localization problem left arm/hand. Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
F^{moderate}	Screening: Observable somatosensory problems. Nothing unusual in Body localisation task and Template matching task. Rubber hand illusion task: Signs of reduced sense of self-awareness; when confronted with rubber hand in task, pt. could not disentangle the fake hand from the own. Pt. was convinced that no rubber hand was present at all.
G^{severe}	Screening: Observable somatosensory and motor problems. Pt. shows expressive language problems. Receptive language seems intact. Pt. can display hostile behavior towards hand. Nothing unusual in Body localisation task and Template matching task. Rubber hand illusion task: Signs of reduced sense of self-awareness; when confronted with rubber hand in tasks, pt. could not disentangle the fake hand from his own. Pt. was convinced that no rubber hand was present at all.
H^{moderate}	Screening: Observable somatosensory problems, however pt. is unaware of the problems. Pt. seemed unmotivated at times. Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
I^{excluded}	Screening: No observable somatosensory problems; no problems in moving both arms/hands. Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
J^{severe}	Screening: Observable somatosensory problems. Observable spasticity in left hand. Pt. reasoned during Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
L^{moderate}	Screening: Observable somatosensory and motor problems. Observable upper-left visual field defect. Works very slowly and is easily distracted. Talkative during tasks. Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
M^{moderate}	Screening: Observable somatosensory and motor problems. Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
N^{moderate}	Screening: Observable somatosensory problems. Observable callus on his hands. Misses the top of his left middle finger. Nothing unusual in Body localisation task, Template matching task and Rubber Hand Illusion.
	** Patient K was excluded from this study due to problems in understanding and is therefore missing in the table.*

SUMMARY OF RESULTS

Body localisation task

Outcome measures: % misestimation width, % misestimation length, overall shape

In general, all groups show the classical distortions (i.e., short fingers, and broadened hands). For the width, analyses revealed no differences between the left and right hand nor between group differences. For the length, analyses revealed that the underestimation of the thumb was less pronounced for the left hand compared to the right hand in only the PT severe group. Analyses revealed that the PT severe group underestimated the ring and the little finger to a larger extent than the PT moderate. The overall shape was statistically similar between hands and between groups.

Case analyses revealed that for the width of the left hand patient A^{severe} (overestimation) and J^{severe} (underestimation) were statistically different from HC. For the length, only patient A^{severe} and $F^{moderate}$ overestimated every finger length, whereas HC underestimated finger length. Relative to HC, the thumb was underestimated by a few patients. With respect to the length for the right hand, patient E^{severe} and patient J^{severe} significantly underestimated their right index finger, middle finger, respectively. Most patients, however did not differ from HC's. Generally, all patients revealed 'the same wider than it is long' ratio, for patient $F^{moderate}$ and $M^{moderate}$ this was more extreme than HC for the right hand.

Template matching task

Outcome measures: % misestimation width, % misestimation length, overall shape

In general, all groups were accurate in estimating the shape of the hand when presented with a visual template of the hand. For *the width and length*, no differences between hands, and groups were found. *The overall shape* was however more distorted for only the severe patients (longer than is wide) as compared to HC. Case analyses revealed that for the width of the left hand patient A^{severe} (underestimation width) and J^{severe} (underestimation width) were statistically different from HC. For the length, only patient A^{severe} trended to overestimate finger length, whereas HC score revealed a near veridical hand estimate. For the right hand, there was a trend for overestimation of the width for patient $C^{moderate}$ relative to controls, and an overestimation of the length for patient $H^{moderate}$. Compared to controls was the shape of the hand longer than is wide for patient A^{severe} (left hand) and J^{severe} (both hands). The shape index for the right hand for PT $L^{moderate}$ was wider than it is long.

DISCUSSION

In the current study we aimed to investigate the effect of chronic somatosensory and or motor loss in the hand, due to stroke, on the representation of our hand (i.e., metric features such as shape and dimensions). Two types of representations were examined in both hands and in two groups; a more visual, explicit representation (Longo and Haggard, 2012) and a more somatosensory, implicit representation (Saulton et al., 2015; Longo and Haggard, 2010). We would like to emphasize that our patient groups are rather small, as such, our small group analyses should be interpreted with caution.

In the implicit body localization task both patient groups and controls showed generally an overestimation of hand width and an underestimation of hand length, indicating that when implicitly prompted about their hand dimensions, both groups show the classical distortions, and similar to what has been previously reported (Longo and Haggard, 2010). Next to the systematic bias that has been observed, it is interesting to note that patients were consistent in their responses. Thus while somatosensory afferents were diminished, or absent in some, they were able to make consistent judgments of their hand shape in the absence of vision, which indicates that they still have access to a multimodal representation of their affected body parts. For the width, analyses revealed no differences between the left and right hand, and no between group differences. The length analyses revealed that the underestimation of the thumb was less pronounced for the left hand compared to the right hand in only the severe group. Results furthermore revealed that the patients in the severe group underestimated the length of the little finger and the ring finger for the right hand to a larger extent than the moderately impaired group. We cannot explain why these two fingers were more affected, but we do know from previous research that unilateral damage can result in bilateral sensory problems (Jones et al., 1989; Knecht et al., 1996; Batelli et al, 2001). The overall shape was statistically similar between hands and between groups. Zooming in on individual cases, differences between individuals and controls do appear. Patient A and J both differ from controls when estimating hand width, although their pattern of results do not match. Patient A greatly overestimates the hand width, and patient J underestimates the hand width. For the length, only patient A and patient F overestimate the length of most fingers, whereas HC underestimate the hand length. Although patient F shows somatosensory problems, they are not as severe as patient A. What is interesting is that both patients show diminished awareness for their affected body part. Patient A suffers from anosognosia for hemianesthesia. She reports hardly any body-related problems. At times she thinks her husbands' hand is her hand, and she is verbally and physically hostile towards it. When confronted with a rubber hand in the RHI patient A could not disentangle the rubber hand from her own hand. We observed that placing the fake hand in an anatomic implausible position did not diminish the subjective experience. Somatic delusions such as somatoparaphrenia are often linked to anosognosia (Vallar & Ronchi, 2008). We also observed diminished awareness of the left arm in patient F throughout the experimental tasks, and likewise when confronted with a rubber hand, patient F could not tell the difference either, and was convinced that no rubber hand was present at all. Perceiving a body part as abnormally large (termed macrosomatognosia) has been linked to body awareness disorders (Pisella et al., 2019; Herbet et al., 2019). Interestingly, the latter study postulates that impaired sensorimotor representation lies at the heart of the clinical characteristics of these disorders, and not a higher cognitive cause per se. It is worth mentioning that the authors were mainly interested in the neuropsychological and neurological profile of fourteen glioma patients, they did not assess underlying mechanisms of the clinical characteristics of body awareness disorders. One patient in their study showed macrosomatognosia, and in the absence of vision his left leg felt disproportionately larger than his right leg. This patient underwent a resection of the precuneus and paracentral lobule, the former being involved in processes such as self-consciousness, engaging in self-related mental representations during rest, and sense of agency (Cavanna, 2006), the latter playing a pivotal role in the somatosensory representation of the leg. For this reason, the authors argued in favour of an impaired sensorimotor representation for macrosomatognosia. Pisella et al., (2019) further argues that damage to the medial part of the parietal lobule, such as the precuneus, affects integration of proprioception (tactile) and visual information in such a way that these proprioceptive and visual experiences diverge from another. This is an important presumption, because typically we integrate senses (visual, tactile, proprioception) in order to establish a sense of ownership over our hand (Botvinick, 1998). When a mismatch is experimentally induced between those senses, it may result in selective fading of the limb. Hogendoorn et al., (2009) induced proprioceptive and visual conflict and found that the mismatch disconnected the two senses which prevented multisensory integration. Subsequently, the brain resolved this conflict by disowning the visible limb. As Pisella and colleagues state, damage to the precuneus may result in proprioceptive and visual divergence. They further argue if additionally, the patient displays a primary somatosensory deficit, macrosomatognosia may be observed. From a clinical perspective then, we would expect macrosomatognosia when a patient displays less awareness over the affected body part, has less hand ownership due to selective fading and on top of that reduced somatosensory input. Unfortunately, we do not possess detailed lesion information from our patients, but we do observe that two patients who experience a disproportionately large hand do have diminished body awareness, report problems in hand ownership ánd also display somatosensory deficits. However, not all patients show this pattern, for instance patient E (clinically) shows diminished hand awareness, reports ownership problems over the affected body part, has somatosensory deficits, but shows no signs of macrosomatognosia. Preliminary results from our lab and a previous report from a patient with a phantom limb (Longo and Haggard, 2012) show that without visual and somatosensory input one is able to form a percept of that limb. These authors attribute their finding to either transcallosal compensation of the healthy limb representation and/or that this representation stems largely from an "innate organization of the body in the brain". A very recent study addressed this notion. These authors studied body size perception in two "deafferentated" individuals, one with acquired somatosensory problems and one patient with congenital absence of somatosensation. Authors found that the patient with congenital somatosensory absence shows less awareness of hand shape and less spatial accuracy in reporting the landmarks of the hand, indicating perception of the hand requires experience of hand action (Miall et al., 2021). In short, our data confirms the presumption of other researchers that body awareness problems and sensorimotor problems can result in body perception problems, such as macrosomatognosia. However, this is not always the case, and the exact mechanism why patients with a similar clinical presentation have a different body percept remains unknown. Functionally we could argue that it makes sense that 'the brain enlarges' the percept of the hands in the absence of vision when one is less aware and had reduced primary sensory input. When vision is absent, a large hand, and thus having a larger safety margin around the hand can maintain bodily integrity when confronted with harm.

In general, all groups were accurate in estimating the shape of the hand when presented with a visual template of the hand. Both patients and healthy controls estimated their hand as near veridical when explicitly prompted about their hand dimensions; both groups show similar results. Previous studies showed that individuals are able to accurately match body shape and size when presented a visual template of their body parts (Longo & Haggard, 2012; Linkenauger et al., 2015). This was expected, since the visual modality of the patient group is still intact and they can gain access to more conscious representations of their body. According to Longo (Longo, 2015; Longo 2017) the representation of our body lies on a continuum, on one end lies the somatotopic maps of the body surface and on the other end a more visually driven, conscious representation of our body. Thus, how we perceive body dimensions depends on different weightings along this continuum. When somatosensory information is available we perceive our hands as highly distorted, however when we move to the other end of the continuum, with visual predominance, we perceive our hands as near veridical. For some patients, somatosensory information was absent, however their vision is intact, and therefore they are able to tap into a conscious representation of their unfelt hand, just as healthy controls are able to. However, and unexpectedly, patients in the severe group perceive the overall shape as more distorted (e.g., longer than it is wide) than HC. One account for this result might be a compensatory mechanism involving tactile-visual remapping. We know that that Weber's illusion (1834/1994) is smaller than the cortical extent, and that tactile size constancy might be achieved by remapping the felt location towards a (more reliable) visual representation of the body (Röder, Rösler, & Spence, 2004; Taylor-Clarke, Jacobsen, & Haggard, 2004; Linkenauger**,** Wong**,** Geuss, Stefanucci, McCulloch et al., 2017). This strong 'visual correction' might be necessary for a highly distorted somatosensory representation. However, in the absence of somatosensory input, which is especially the case in the group of severe patients, the visual rescaling process might then overshoot the somatosensory estimation, resulting in overcorrecting the width since the receptor density is the highest there. Additionally, we can also conclude from this finding that somatosensory deficits can influence the hand perception crossmodally by modulating visual percepts of the body.

Next to the quantitative data, it is particularly noteworthy that when screened and explicitly asked, 46 percent of our included patients reported diminished ownership over the left hand. Additionally, 38 percent of our included patients reported negative emotions regarding the affected limb. For some patients it even went further than just negative thoughts, such as hatred (e.g., swearing at hand), physical violence (e.g., beating or thrashing the hand). This behaviour has been coined misoplegia by Critchley (1974), and refers to a morbid dislike of the hemiplegic limbs in patients after stroke. Misoplegia might stem from unawareness, indifference, lack of ownership in these patients (Pearce, 2007). Follow up screening by a neurologist should be aware of these kind of problems and questions about attitudes about their body should be protocol. Although no rehabilitation is yet available for ownership problems, psychological support might offer some alternative support in changing maladaptive attitudes towards the affected body part.

Taken together, with respect to the implicit body perception as measured with the body localization task patients with moderate to severe sensory impairments have access to a multimodal representation in the absence of somatosensory functioning. Generally, both patients and controls show the classical distortions; short, wide hands. A few patients experienced a disproportionally large hand. This finding seems to be linked to diminished body awareness, and sensorimotor deficits. With respect to the more conscious body perception, as measured with the template matching task we conclude that in general most patient had a veridical percept of their hand. Surprisingly, patients in the severe group perceived the overall shape as to be longer than it is wide (opposite to the somatosensory representation), we attribute this finding to the process of visual-tactile remapping. Lastly, 38 percent of our included patients showed negative affect towards the arm and report problems in how they perceive their bodies. Follow-up neurological examination should address standard questions about body attitudes.

SUPPLEMENTARY MATERIAL A

Prior to initiation of the experimental tasks, a short interview about their symptoms was conducted, followed by the screening tasks (for the screening scores see Table 3).

Table A1. *Key reported problems by the patients on our somatosensory screening questionnaire*[1]*. Note that these answers are introspective.*

	Somatosensory	**Motor**	**Ownership**	**Mood**
Patient A		x	x	x
Patient B		x		
Patient C				
Patient D	x	x		
Patient E	x	x	x	x
Patient F	x	x	x	x
Patient G	x	x	x	
Patient H				
Patient I	x		x	x
Patient J	x	x	x	x
Patient L	x			
Patient M	x	x		
Patient N				
Total	54%	62%	46%	38%

[1] Key domains in questionnaire: Somatosensory problems consisted reduced sense of touch, problems in localizing touch, hypersensitivity and experiencing tingling sensations. Motor consisted of paralyses of one side of the body (i.e., hemiplegia), fine motor skills problems and motor control problems. Ownership problems consisted problems in experiencing the affected limb(s) as one's own, confusing another person's limb(s) with their own affected limb(s) and the incorrect idea of missing a limb(s). Mood problems consisted of the experience of strong positive or negative feelings against the affected limb(s), naming the affected limb(s) and talking to the affected limb(s).

SUPPLEMENTARY MATERIAL B

Below we present the data of the individual cases against healthy controls on the body localisation test, the template matching test and the rubber hand illusion. For each outcome measure we present a table providing data and test-statistics of the left hand (left) and the right hand (right).

BODY LOCALISATION TEST

Misestimation of the width of the left and right hand.

Table B1. *Mean (M) of the width for the left hand (LH) and right hand (RH) for HC (group-level) and PT (individual level) on the body localisation Task. Average scores of HC are indicated in bold. Individual scores and statistics of the PT are given below (patient A – N). Patients whom scored different from the HC's are indicated in blue font colour.*

		t	*p*		*t*	*p*
Controls *(N= 29)*	**M= 82.03** **(SD= 38.82)**	-	-	**M= 86,88** **(SD= 60,29)**	-	-
pt A	166.67	2.144	.041	n.a.	n.a.	n.a.
pt B	101.56	.495	.625	152.38	1.068	.295
pt C	151.61	1.762	.089	33.33	-.873	.390
pt D	103.03	.532	.599	92.75	.096	.924
pt E	12.07	-1.772	.087	17.24	-1.136	.266
pt F	70.15	-.301	.766	83.05	-.062	.951
pt G	38.03	-1.114	.275	-1.45	-1.440	.161
pt H	26.76	-1.400	.173	39.73	-.769	.448
pt I	135.29	1.349	.188	115.79	.471	.641
pt J	-53.23	-3.426	.002	74.60	-.200	.843
pt L	46.15	-.909	.371	7.35	-1.297	.205
pt M	88.52	.164	.871	192.06	1.715	.097
pt N	87.50	.139	.891	137.50	.825	.416

Misestimation of the length of the left hand.

Table B2. *Mean (M) of the length for the* *<u>left hand</u>* *(L) for HC (group-level) and PT (individual level) on the body localisation Task. Average scores of HC are indicated in bold. Individual scores and statistics of the PT are given below (patient A – O). Patients whom scored different from the HC's are indicated in blue font colour.*

	L little finger			L ring			L middle			L index			L thumb		
(Controls N = 29)	**M= -27,99 (SD= 29,83)**	*t*	*p*	**M= -43,98 (SD= 24,08)**	*t*	*p*	**M= -30,24 (SD= 21,49)**	*t*	*p*	**M= -28,46 (SD= 20,18)**	*t*	*p*	**M= -5,68 (SD= 22,26)**	*t*	*p*
pt A	133.82	5.333	.000	84.88	5.261	.000	101.1	6.009	.000	125.3	7.491	.000	260.47	11.755	.000
pt B	-22.67	.175	.862	-36.96	.287	.777	-21.00	.423	.676	-45.56	-.833	.412	-9.80	-.182	.857
pt C	-29.33	.044	.965	-46.46	-.101	.920	-41.58	-.519	.608	-31.46	-.146	.885	-37.74	-1.416	.168
pt D	-49.28	-.702	.489	-65.00	-.858	.398	-36.89	-.304	.763	-31.46	-.146	.885	-13.11	-.328	.745
pt E	-68.66	-1.340	.191	-75.86	-1.302	.204	-70.97	-1.863	.073	-63.41	-1.703	.100	-81.13	-3.333	.002
pt F	45.16	2.411	.023	12.50	2.306	.029	67.39	4.467	.000	5.95	1.676	.105	35.09	1.801	.083
pt G	-31.88	-.128	.899	-44.71	-.030	.976	-6.86	1.070	.294	-6.59	1.066	.296	20.00	1.134	.266
pt H	-7.81	.665	.511	-22.37	.882	.385	-13.10	.784	.440	-38.27	-.478	.636	-24.56	-.834	.411
pt I	-50.00	-.725	.474	-60.71	-.683	.500	-47.31	-.781	.441	-21.18	.355	.725	-34.04	-1.253	.221
pt J	-67.11	-1.289	.208	-75.25	-1.277	.212	-56.31	-1.193	.243	-48.94	-.998	.327	-64.71	-2.607	.014
pt L	-24.32	.121	.905	-44	-.001	.999	-45.1	-.680	.502	-36.96	-.414	.682	-56.86	-2.261	.032
pt M	-46.91	-.624	.538	-58.25	-.583	.565	-52.73	-1.029	.312	-52.94	-1.193	.243	-36.36	-1.355	.186
pt N	-2.82	.830	.414	-26.6	.710	.484	-25.53	.215	.831	-30.11	-.080	.936	0	.251	.804

Misestimation of the length of the left hand.

Table B3. *Mean (M) of the length for the* *<u>right</u>* *hand (R) for HC (group-level) and PT (individual level) on the body localisation Task. Average scores of HC are indicated in bold. Individual scores and statistics of the PT are given below (patient A – O). Patients whom scored different from the HC's are indicated in blue font colour.*

	R little finger			R ring			R middle			R index			R thumb		
Controls (N= 29)	M = -28.83 (SD=21.85)	t	p	M= -43.92 (SD= 17.42)	t	p	M= -26.89 (SD=20.93)	t	p	M= -25.91 (SD=26.70)	t	p	M= -7.54 (SD=30.95)	t	p
pt A	n.a.			n.a.			n.a.			n.a.			n.a.		
pt B	-10.96	.804	.428	-32.29	.656	.517	-11.65	.716	.480	-21.74	.154	.879	-8.77	-.039	.969
pt C	-18.18	.479	.636	-35.05	.501	.621	-2.83	1.130	.268	-6.74	.706	.486	-11.32	-.120	.905
pt D	-25.33	.157	.876	-45.10	-.067	.947	-26.92	-.001	.999	-35.48	-.352	.727	21.57	.925	.363
pt E	-46.27	-.785	.439	-58.62	-.830	.414	-64.52	-1.768	.088	-85.37	-2.190	.037	-30.19	-.720	.478
pt F	9.72	1.735	.094	-9.20	1.960	.060	0.00	1.263	.217	7.32	1.224	.231	37.04	1.416	.168
pt G	-70.27	-1.865	.073	-77.08	-1.872	.072	-28.16	-.060	.953	2.20	1.035	.309	-28.36	-.661	.514
pt H	-26.23	.117	.908	-41.56	.133	.895	-3.70	1.089	.285	-23.75	.080	.937	5.56	.416	.680
pt I	-25.76	.138	.891	-40.96	.167	.869	-39.13	-.575	.570	-35.90	-.368	.716	-38.00	-.968	.342
pt J	-54.67	-1.163	.255	-64.21	-1.145	.262	-72.12	-2.125	.043	-52.22	-.969	.341	8.20	.500	.621
pt L	-25	.172	.864	-45.45	-.086	.932	-43.14	-.763	.452	-22.34	.131	.896	-21.43	-.441	.662
pt M	-58.75	-1.346	.189	-67.96	-1.357	.186	-61.61	-1.631	.114	-45	-.703	.488	-13.11	-.177	.861
pt N	-16.22	.567	.575	-34.04	.558	.582	-14.29	.592	.559	-26.88	-.036	.972	45.28	1.678	.104
pt O	-35.21	-.287	.776	-47.72	-.214	.832	-42.55	-.736	.468	-40	-.519	.608	-13.21	-.180	.858

Shape indices

Table B4. *Mean (M) of the Shape index for the left and right hand for HC (group-level) and PT (individual level) on the body localisation Task. Average scores of HC are indicated in bold. Individual scores and statistics of the PT are given below (patient A – N). Patients whom scored different from the HC's are indicated in blue font colour.*

BMT	**Normalized SI LH**			**Normalized SI RH**		
Controls (N= 29)	*M= 2.88* *SD= 1.15*	t	p	*M = 2.77* *SD= 1.28*	t	p
pt A	1.32	-1.334	.19	n.a.	n.a.	n.a.
pt B	2.55	-.282	.78	2.87	.077	.94
pt C	4.33	1.240	.23	1.37	-1.075	.29
pt D	3.23	.299	.77	2.62	-.115	.91
pt E	3.86	.838	.41	3.30	.407	.69
pt F	1.02	-1.590	.12	1.83	-.722	.48
pt G	1.48	-1.197	.24	1.37	-1.075	.29
pt H	1.45	-1.223	.23	1.46	-1.006	.32
pt I	4.42	1.317	.20	3.57	.614	.54
pt J	1.09	-1.530	.14	6.35	2.750	.01
pt L	2.66	-.188	.85	1.88	-.684	.50
pt M	3.99	.949	.35	7.67	3.764	.00
pt N	2.53	-.299	.77	2.77	.000	1.00

TEMPLATE MATCHING TASK

Misestimation of the width and the length of the left and right hand.

Table B5. *Mean (M) of the width for the left (LH) and right hand (RH) for HC (group-level) and PT (individual level) on the template matching Task. Average scores of HC are indicated in bold. Individual scores and statistics of the PT are given below (patient A – N). Patients whom scored significantly different from the HC's are indicated in blue font colour.*

	WIDTH LH			WIDTH RH		
Controls *(N= 29)*	M= 0.997 (SD= 0.090)	*t*	*p*	M= 0.992 (SD= 0.090)	*t*	*p*
pt A	0.82	-1.934	.063	0.97	-.240	.812
pt B	0.845	-1.661	.108	0.925	-.732	.470
pt C	1.065	.743	.464	1.16	1.835	.077
pt D	1.025	.306	.762	0.975	-.186	.854
pt E	1.04	.470	.642	1.04	.524	.604
pt F	0.96	-.404	.689	1.075	.907	.372
pt G	0.98	-.186	.854	0.995	.033	.974
pt H	1.00	.033	.974	1.01	.197	.846
pt I	1.015	.197	.846	1	.087	.931
pt J	0.715	3.081	.005	0.87	-1.333	.193
pt L	1.12	1.344	.190	0.955	-.404	.689
pt M	0.905	-1.005	.323	1.015	.251	.803
pt N	0.935	-.677	.504	0.995	.033	.974

Table B6. *Mean (M) of the length for the left (LH) and right hand (RH) for HC (group-level) and PT (individual level) on the template matching Task. Average scores of HC are indicated in bold. Individual scores and statistics of the PT are given below (patient A – N). Patients whom scored significantly different from the HC's are indicated in blue font colour.*

	LENGTH LH			LENGTH RH		
Controls *(N = 27)**	1.032 (SD= 0.101)	*t*	*p*	1.037 (SD= 0.094)	*t*	*p*
pt A	1.22	1.828	.079	0.98	-.595	.557
pt B	1.085	.515	.611	1.11	.763	.453
pt C	1.115	.807	.427	1.175	1.442	.161
pt D	1.045	.126	.900	1.07	.345	.733
pt E	1.09	.564	.578	1.05	.136	.893
pt F	1.03	-.019	.985	0.95	-.909	.372
pt G	1.11	.758	.455	1.105	.710	.484
pt H	1.12	.856	.400	1.24	2.121	.044
pt I	0.975	-.554	.584	0.98	-.595	.557
pt J	1.04	.078	.939	1.14	1.076	.292
pt L	0.875	-1.526	.139	1.06	.240	.812
pt M	1.12	.856	.400	1.02	-.178	.860
pt N	1.09	.564	.578	1.045	.084	.934

* *For the length, data of first two individuals was not stored*

Shape indices

Table B7. *Mean (M) of the Shape index for the left and right hand for HC (group-level) and PT (individual level) on the body localisation Task. Average scores of HC are indicated in bold. Individual scores and statistics of the PT are given below (patient A – N). Patients whom scored different from the HC's are indicated in blue font colour.*

TMT	**Normalized SI LH**			**Normalized SI RH**		
Controls (N= 27)	*M= 0.97* *SD= 0.10*	t	p	*M = 0.97* *SD=* 0.09	t	p
pt A	0.67	-2.946	.01	0.99	.218	.83
pt B	0.78	-1.866	.07	0.83	-1.528	.14
pt C	0.96	-.098	.92	0.99	.218	.83
pt D	0.98	.098	.92	0.91	-.655	.52
pt E	0.95	-.196	.85	0.99	.218	.83
pt F	0.93	-.393	.70	1.13	1.746	.09
pt G	0.88	-.884	.38	0.90	-.764	.45
pt H	0.89	-.786	.44	0.81	-1.746	.09
pt I	1.04	.687	.50	1.02	.546	.59
pt J	0.69	-2.750	.01	0.76	-2.291	.03
pt L	1.28	3.044	.01	0.90	-.764	.45
pt M	0.81	-1.571	.13	1.00	.327	.75
pt N	0.86	-1.080	.29	0.95	-.218	.83

Chapter 7

The man who lost his body: Suboptimal multisensory integration yields body awareness problems after a right temporoparietal brain tumour

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Published in: Journal of Neuropsychology, 2019

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ABSTRACT

Reports on patients who lack ownership over their entire body are extremely rare. Here we present patient SA who suffered from complete body disownership after a tumor resection in the right temporo-parietal cortex. Neuropsychological assessment disclosed selective bilateral ownership problems, despite intact primary visual and somatosensory senses. SA’s disownership seems to stem from a suboptimal multimodal integration, as shown by the rubber hand illusion and the beneficial effect during and after simple exercises aiming at multisensory recalibration.

INTRODUCTION

Following brain damage patients can experience that parts of their body do not belong to themselves. It usually concerns the affected limb contralateral to the affected hemisphere, typically the (hemiparetic) left limb after right hemispheric damage (Nightingale 1982, Baier et al., 2008, Vallar 2009, Gandola et al., 2012). Vallar & Ronchi (2009) suggested that disownership of limbs in patients with somatoparaphrenia, a misidentification and confabulation of limbs, could be the result of a “defective” integration of visual, tactile and proprioceptive information in concurrence with problems in the spatial representation of the body. The integration of this information has been associated with the inferior posterior parietal cortex (Dijkerman & de Haan 2007, Kammers et al., 2009) and the ventral premotor cortex (Ehrsson et al., 2004, Zeller et al., 2011). While disownership over one body part has been reported regularly, patients who lack ownership over their entire body are extremely rare. Here we present a 46- year-old man, patient SA, whom suffered from a diminished sense of ownership over his complete body. The main aim of this study was to examine the (cognitive) mechanism underlying his subjective reports of body disownership.

Patient characteristics

Patient SA was a 46-year old man who was diagnosed five years before the current consultation with an intraventricular brain tumor, located in the right posterior part of the lateral ventricle (Figure 1). The tumor was an incidental finding on a cranial CT scan, performed after an unrelated head trauma. In retrospect, SA reported that problems in body representation developed gradually before the first consultation (> five years ago). On neurological examination no focal deficits were present. Within two months after the diagnosis, SA underwent an elective transcortical resection of the tumor through the right parietal lobe. Neuropsychological examination five months after resection stated that ‘despite problems in orientation in space (i.e., navigation) and time, the neuropsychological assessment shows overall a strongly analytic and beyond average cognitive profile’ (Table 1 in supplementary material B). Importantly, performance on several other spatial tests including left-right orientation, judgment of line orientation and line bisection were unimpaired suggesting that the spatial problem was specific for navigation and that there was no general spatial perception deficit. Although he did also report problems in the feeling of body ownership, this was not examined at that time. At the time of the current study, 5 years after his initial diagnosis and surgery, SA reported that his problems in body ownership (see subjective reports below) had become more pronounced. No new focal neurological deficits were identified at the time of the study compared to previous examination.

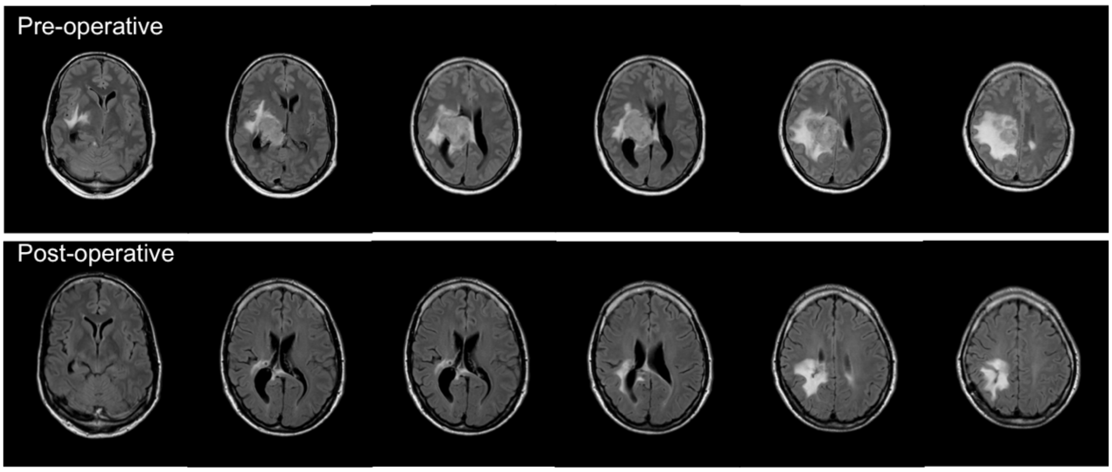

Figure 1. MRI scans with T2-weighted images with fluid attenuated inversion recovery (Flair) in axial plane. The upper row represents pre-operative images showing a circumscript right intraventricular lesion with dimensions 5x4x4 centimeters (with T1 enhancement after gadolinium administration; not shown). The lesion is accompanied by a large area of subcortical edema extending cranially from the tumor as well as some mesiotemporal edema. The bottom row represents post-operative images (6 months prior to the current study). These images show residual right parietal hyper intensities (gliosis) and a small area of postoperative cortical changes located posteriorly in the parietal lobe. Some residual T1 gadolinium enhancement of the lateral ventricle wall was seen (unchanged compared to previous postoperative MRI scans; images not shown). Note that images are in radiological orientation (left side of the image is the right side of the brain).

Subjective reports

SA reported absence of ownership over his whole body, i.e., not being able to recognize, feel or experience his body as its own, despite the fact that he knows it is his own. Although disownership affects his whole body, problems were most pronounced in both hands, left more than right, and while driving a car: “As if I am in a shell, a passenger whilst driving myself.” There were no problems in motor planning or executing, nor were there any reports of somatosensory problems. He was able to do all daily activities and played tennis. SA was able to recognize his body as his own when looking at this body. Without vision, he reported that his body became 'lost'; unable to mentally build an image of the configuration of his body parts (e.g., where his arm is attached to his body), and was missing the sense that he owned a body. In a mirror, this sense of “disintegration” diminishes, however the sense of disownership remains. Other reported problems include problems in left/right discrimination and problems in space perception in general (e.g., estimating the width of a quay). Of these aforementioned complaints, the sense of disownership has the greatest impact on his daily activities and reduces quality of life. SA did report mood-problems and is familiar with depressive episodes for which he receives therapy. He further stated that these episodes did not and do not modulate the feelings of body disownership, and thus seem unrelated.

Basic sensory and neuropsychological testing

Following his subjective reports, we examined SA twice; the first and second examination was separated by two weeks. In both examinations, we prepared an individually tailored test-battery covering the aspects of patient's complaints (i.e., body representation and space perception), see Table 2.

Table 1. Test-battery and underlying mechanism for all sessions 0 (baseline), 1 & 2 covering patients' complaints in body representation.

Test*	Mechanism/aim	Session	Impaired/not impaired
Draw-a-person task	semantic knowledge of body	1	not impaired
Subjective sense of ownership	subjective sense of ownership	1 & 2	impaired
Tactile pointing task	metric aspects of body	1	not impaired
Body localization task	structural body representation	1	not impaired
Implicit relative position sense task	spatial configuration of body	1	not impaired
Rubber hand illusion	body ownership	1 & 2	*see results*
Finger gnosis	structural body representation	0	not impaired**
Proprioception	primary somatosensory function	0	not impaired
Two-point discrimination	primary somatosensory function	0	not impaired

See supplementary material A for more detailed information on stimuli, test and test procedures. At the time of resection there were no neuropsychological (i.e., memory, executive functioning, visuoperception, language) and psychiatric deficits (formally tested). ** There were subtle signs of finger agnosia shortly after the resection.

Primary somatosensory function

Tests for relative position sense and two-point discrimination were administered for both hands (according to Winward 2002), which showed no indication of impairments in proprioception, and tactile acuity.

Spatial and structural body representation tasks

Results on the tactile pointing, body localization and implicit relative position sense (see supplementary material A for detailed information and test instructions) suggested no problems in most aspects of his body representation, hence the spatial, configural and metric aspects as well as conscious perceptions, attitudes, and beliefs concerning a human body seem intact, and therefore do not contribute to his feelings of body disownership. These findings are in line with the 'Draw-a-person-task' in which he was able to configure what a healthy person should look like. However, when he had to draw how he experienced his own body, he only drew the body parts (i.e., the hands) that were visible for him (Figure 2A, and B respectively).

Body ownership

The overall subjective experience of ownership was measured with a visual analogue scale (VAS), and the Rubber Hand Illusion (RHI). These were compared to the data of six[4] healthy (gender and age matched (average age 46.5 (SD=7.7)) controls. Design and set-up for the VAS and RHI in controls was identical to that of SA. Statistical analysis was performed on the VAS and on both outcome measures of the RHI by frequentist statistics with single case-control analyses (Crawford and Howell, 1998) and with Bayesian Single Case Method analyses.

The VAS showed that SA reported - when asked to what extent his hands felt as his own - hardly any feelings of ownership over both hands, as opposed to controls (see Table 2 for statistical comparison with healthy controls).

Table 2. *Subjective experience of hand (i.e., left, right) ownership (in %) indicated on a Visual Analogue Scale (VAS) for patient SA and controls for both session (s) 1 and 2.*

	patient SA		controls*	
	s1	s2	s1	s2
left hand	5***	40***	100	100
right hand	32***	43***	100	100
left hand exercise**	n/a	77***	n/a	100
right hand exercise**	n/a	78***	n/a	100

** All controls scored 100 (SD = 0), in order to be able to compute Crawfords statistics, SD was set at 1 for all tests.*

*** feeling of ownership during the exercises. n/a = not applicable, since these measures were not administered during the first session.*

**** significantly different from controls (p < .0001)*

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[4] One control was excluded, because he did not fully understand the test instructions, the questionnaires and the subsequent exercises.

In addition, we presented the classic RHI (see Botvinick & Cohen, (1998) for a detailed procedure; set-up adopted from Kammers, de Vignemont, Verhagen, & Dijkerman (2009) plus an extra condition where he only had to look at the rubber hand (visual only). On each trial, except for the visual only, the rubber hand and the invisible hand are stroked for 90 seconds, either synchronously or asynchronously. Commonly, the synchronous visuotactile stimulation causes the highest feelings of ownership Botvinick & Cohen, (1998). Mere visual exposure to a rubber hand is thought to lead to some embodiment, but insufficient to reach full-blown embodiment over the rubber hand in healthy participants (Longo et al., 2008; Ferri et al., 2013). Asynchronous stimulation would result in the least illusion and usually serves as a control condition. Indeed this is exactly what we found in our control group for session 1 (Figure 2C, D for statistics). Relative to the control group SA experienced an increased sense of ownership over the rubber hand, as reflected on both outcome measures (e.g., (behavioural) proprioception and (subjective) embodiment questionnaire). Moreover unlike the controls, there was no difference between synchronous stroking and visual input only on both measures, suggesting that SA did not benefit from multisensory integration (Figure 2C,D). In session one (S1, light pattern) SA scores far above the illusion threshold (5) for the asynchronous and visual condition in the subjective measure. Controls (S1), however, do not score above 5 in these conditions, which is the usual pattern of results (Kammers et al., 2009). In fact, SA reported that the stroking in the synchronous condition interfered with the illusion. Even more so, he reported that visually focusing for 90 seconds created the feeling "that this rubber hand is attached to my body, which I don’t experience with my real hand.” Statistical analyses confirm this pattern of results, especially for the proprioceptive drift measure. Analyses revealed, as expected, a significant difference between controls and the patient for the visual condition (Bonferroni corrected p-values in Figure C,D), and a near significant result for the synchronous condition. This was however not the case for the subjective measure, probably due to small sample size. Additional Bayesian Single Case Method analyses revealed that the estimated percentage of the control population that would obtain a score lower than SA ranges from 67% to 89% for the conditions in the subjective measures and from 86% to 100% for the behavioral measures. Thus, taking the frequentist approach and the Bayesian together, these results indicate that SA overall has a heightened susceptibility for the Rubber Hand Illusion in session 1, which is most pronounced in the visual condition.

For the following weeks, we recommended (as well for the controls) some simple exercises to SA consisting of touching and simultaneously looking at his body through a mirror 3 x 5 minutes a day for two weeks. The rationale behind this was taking advantage of his reliance on vision by making use of a mirror and simultaneously stimulate the intact afferent input by touching his limbs. Additionally, viewing the self from third-person perspective might reinstate ownership by incorporating other (less affected) body parts, such as face and trunk (Fotopoulou et al., 2011).

Two weeks later we applied a subset of the tests again (Table 1). SA's feelings of subjective ownership had changed profoundly, which is outlined Table 2 (s2). Remarkably, when asked how much ownership he experienced during these exercises he reported almost complete ownership. This leads to the compelling idea that just two weeks of simple multisensory stimulation improved feelings of ownership. We presented the RHI again, and surprisingly the experience of ownership dropped in the visual condition (as opposed to the first test-session and other conditions) for both measurements; the pattern now resembled that of a healthy control participant. Statistically, results resembled the first session (Figure 2, C and D), except that the visual condition was near significant between the controls and the patient. Additionally, we added a slow stroking (range of 1–10 cm/s) affective touch condition, which has been previously correlated with pleasant emotion and may facilitate the brain's ability to construct a sense of body ownership (Van Stralen et al., 2014; Crucianelli et al., 2014). During this condition, both measurements (Figure 2D, 2E), but particularly his verbal reports indicate that he embodied the rubber hand the most, "…this seems more like my own hand than the experience in the other conditions. Really 100%! I had no idea where my own hand was." This was confirmed by statistical analyses (Figure 2 C,D).

Finally, we analyzed whether the difference between session 1 and 2 for all the conditions (i.e., synchronous, asynchronous, visual) in SA was significantly greater than the difference observed in controls. Here we found that only for the proprioceptive drift in the visual only condition SA's difference was significantly greater than controls $t = -4.131$, $p = 0.01$, indicating a significant drop in the second session for the visual condition only for SA.

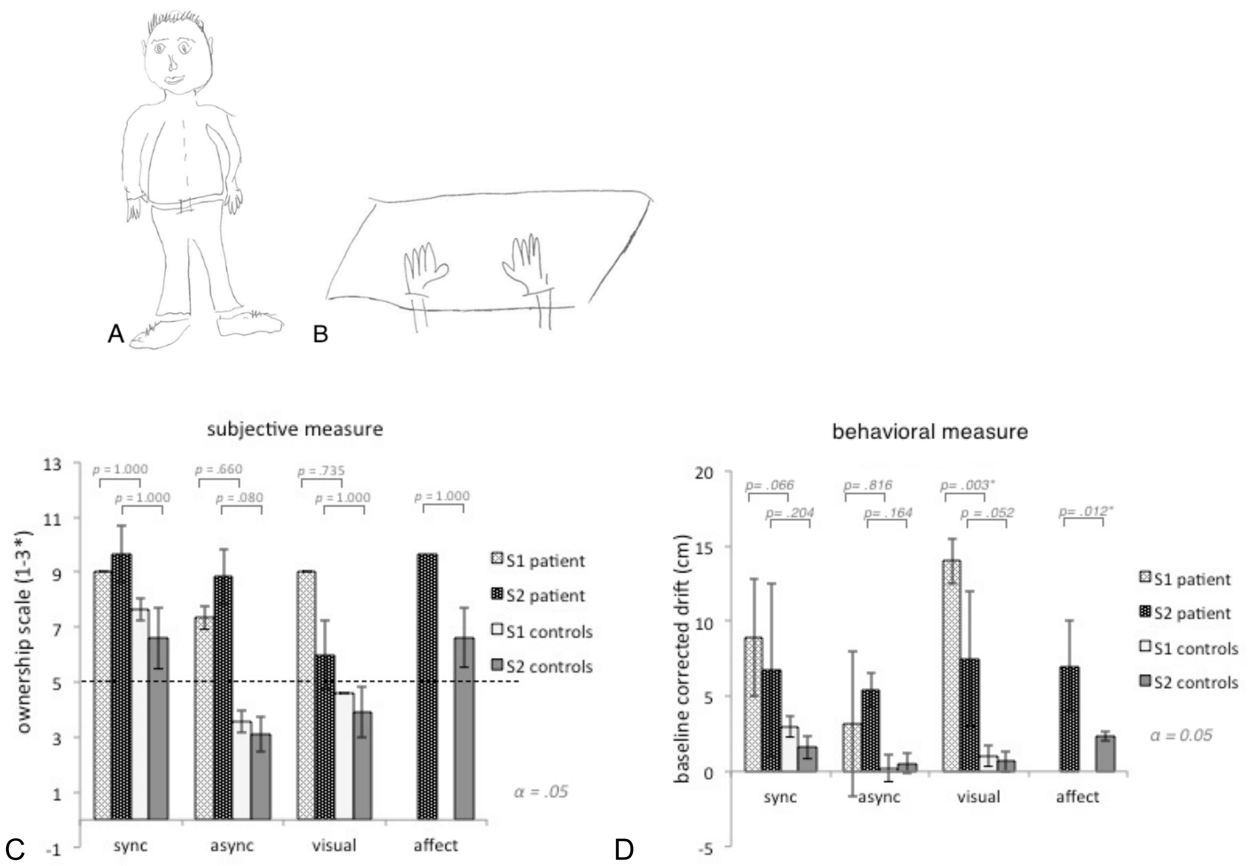

Figure 2. A Left panel: drawing of a physical human body and (right panel) drawing of own experienced body. When instructed to draw a person, he drew an appropriately sized body with correctly attached limbs, indicating intact semantic knowledge of the configural layout of a human body. However, when instructed to draw the experienced own physical body, he initially hesitated and needed further encouragement. SA reported that he was unable to feel the presence of his entire body (including his hands) when he did not look at his body. Looking at a part of his body, increased a feeling of ownership over this part of the body. He then drew a pair of detached arms and hands, since that is the only body part he saw when looking at the table surface (Figure 2B). What is particularly striking is that this drawing is indicative of the reports of the patient; it seemed as if he could only draw what he saw, suggesting reliance on vision without incorporating the other senses which are necessary for ownership (i.e. proprioception, touch) (Vallar & Ronchi, 2009). All controls drew two similar persons. 2C. Average subjective feeling of ownership for SA and controls ('ownership scale' (average Q1-3) of the Embodiment questionnaire), for the stimulated left hand in the synchronous, asynchronous, visual and, affective (only session 2) condition for both test-sessions. For 2C and D: Error bars represent within subject error in SA, and between subject error in controls. * In the visual only condition only 1 (out of 3) questions could be answered, the other 2 questions required tactile input. 2D. Average baseline corrected (post – pre-session) proprioceptive drift (in cm) for all conditions for the left hand for SA and controls.

Discussion and conclusion

Our observations suggest that right temporo-parietal lesions can lead to bilateral body ownership deficits. The problems in body ownership cannot be explained by impairments in the primary somatosensory or motor functioning, nor by a general spatial perceptual deficit. Although the patient did show navigation deficits, his performance on several other spatial tasks was unimpaired. Furthermore, there were no indications that the structural, semantic or spatial body representation was impaired. Analyses confirm that SA has a heightened susceptibility to gain ownership over a foreign hand. This is in line with previous studies that found a stronger illusion for the contralesional hand after acquired brain injury (Van Stralen et al., 2013, Burin et al., 2015, Zeller et al., 2011, White et al., 2017; Llorens 2017). Previous studies have suggested that a stronger illusion in patients with body ownership impairments is a result of a problem in the integration of contralesional afferent and efferent motor signals, since patients with body ownership deficits usually suffer from sensorimotor impairments (Burin et al. 2015). However, patient SA did not suffer from sensorimotor deficits, suggesting that body ownership impairments are not a consequence of a disturbed processing of motor signals. Indeed, a previous study of our lab also found a stronger RHI in a patient with body ownership impairments, but without sensorimotor impairments (Van Stralen et al. 2013). Secondly, the finding that the RHI was most pronounced during visual exposure (as opposed to the synchronous and asynchronous stimulation), ánd that SA did not differentiate between synchronous and asynchronous stimulation suggests that SA did not benefit from multisensory information, but may rely on vision i.e., ‘what he sees’ instead when processing bodily information. Previous studies have also found that asynchronous stimulation, usually considered as a control condition, elicited the RHI to a similar extent as synchronous stimulation in stroke patients (White et al. 2017, van Stralen et al. 2013). The current study, as well as a previous study on a patient with body ownership impairment (Van Stralen et al. 2013) shows that visual exposure seems to elicit a stronger illusion opposed to multimodal (synchronous and asynchronous) stimulation. It remains inconclusive where this suboptimal integration stems from. White et al., 2017 propose a plausible explanation in patients wíth hemiplegia, and state that these patients might have a problem in detecting asynchrony, that is, somatosensory (as opposed to visual) signals are delayed and as a resultant more weight is given to visual information. Despite intact primary sensory signals, SA’s results do follow a similar pattern where he relies more on what he sees rather than the combination of what he sees and feels, indicating suboptimal multisensory integration. Multisensory integration and body ownership have been associated with the posterior parietal cortex (see Stein et al., 2008 and Tsakiris et al. 2008 for a review), which is in accordance with site of meningioma and resection. Simple exercises involving visual input about the body from a third person perspective combined with tactile stimulation seem to improve body awareness. Furthermore, interoceptive signals, such as affective touch, are able to boost feelings of ownership (Van Stralen et al. 2014) and have been associated with the right insula cortex. Affective touch seemed to additionally reinstate body ownership in patient SA and might facilitate limb-ownership in general.

SUPPLEMENTARY MATERIAL A

Stimuli, tests and procedures

All measurements were conducted in a sound-attenuated room. Patient SA was seated as comfortably as possible. The whole test procedure lasted for 2 hours.

Draw-a-person task. In the person drawing task he was presented a sheet of paper and had to draw a physical human body and in the second trial their own body. The drawings were subjectively evaluated by three independent investigators and were qualified as impaired or unimpaired.

Subjective sense of ownership task. Patient SA was presented a VAS ranging from 0-100% and had to indicate the subjective sense of ownership over both the left and the right hand. Outcome measure was subjective sense of ownership in %.

Tactile pointing task. In the tactile pointing task the experimenter touched the left and right hand briefly with a pen. Patient SA had to point to that location as fast and accurate as possible. Outcome measures were error displacement from the touched location in mm.

Implicit relative position sense task. In this test, SA was placed in two different positions. Thereafter the examiner asked questions about the relative position between two limbs. Outcome measure was number of correct responses, and was qualified as impaired or unimpaired.

Rubber hand illusion (RHI) task. SA was presented with the classic rubber hand illusion (see Botvinick & Cohen, (1998) for detailed procedure). We added an extra condition to the classic procedure, that is, the visual condition. In this condition SA. had to look at the rubber hand for 90 seconds. Outcome measures for all conditions were subjective experience of ownership reflected in an embodiment questionnaire (10 point Likert scale) and the proprioceptive drift in cm (difference score between the pre- and post illusion session).

SUPPLEMENTARY MATERIAL B

Table 1. *Results on neuropsychological examination 5 months after tumor resection.*

Test	**Percentile/score***
Cognitive Screening test	
Mini Mental State Examination	29/30
Language	
Boston naming task	80th percentile
Word Fluency	80th percentile
Working memory	
Digit span(WAIS-III)	41st percentile
Corsi Block tapping Test	10-20st percentile
Memory	
Rey Auditory Verbal Learning Test	
immediate recall	69th percentile
delayed recall	54th percentile
Recognition	30/30[9] (qualified as not impaired)
Location Learning Test	
immediate recall	40th -50th percentile
learning index	60th -70th percentile
delayed recall	30th -85th percentile
Rivermead Behavioral Memory Test	
story immediate recall	16th percentile
story delayed	4th percentile
Visual perception	
Benton Judgment of Line Orientation	> 86th percentile
Benton Facial recognition test[14]	88th -97th percentile
Schenkenback Line Bisection	average -2.75 deviation (left) (qualified as not impaired)
Cortical Vision Screening	69/70 (qualified as not impaired)
Facial expression of Emotion	32/36 (qualified as not impaired)
Stereognosis (object/drawing)	8/8 (qualified as not impaired)
Tactile pointing	left, 2 cm, right 1.9 cm (qualified as not impaired)
Finger gnosis	qualified as below average
Virtual Reality Tubingen	
Scene recognition	94% (qualified as not impaired)
Route continuation	14% (qualified as impaired)
Route order	6 (qualified as below average)
Roadmap	17/30 (qualified as impaired)
Body related perception	
Bergen right left discrimination test	144/144 (qualified as not impaired)
Goldenberg ideomotor Apraxia	20/20 (qualified as not impaired)

Speed processing	
Trail Making Test A	73rd percentile
Trail Making Test B	79th percentile
Stroop colour-word-test	
card I,II,III	38th, 50th, 96th percentile
Executive functioning	
The Hayling and Brixton test	99th percentile
Behavioral Assessment of dysexecutive Syndrome	
Key search	Profile score 3 (qualified as not impaired)
Zoo map	profile score 2 (qualified as not impaired)

**For some scores no percentile scores were available, we then added the raw scores and the qualitative interpretation of the clinical neuropsychologist.*

Chapter 8

Transcranial direct current stimulation to the parietal cortex in hemispatial neglect: A feasibility study

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Published in: Neuropsychologia, 2015

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ABSTRACT

Objectives: Prior research suggests that dampening neural activity of the intact, presumably overactive hemisphere, combined with increasing neural activity in the damaged hemisphere, might restore cortical interhemispheric balance and reduce neglect. In the present study we repeatedly applied a relatively new technique, transcranial direct current stimulation (tDCS), to the posterior parietal cortex to modulate spontaneous neural activity levels in a polarity dependent fashion to find evidence for improvements in severe hemispatial neglect in chronic patients. Methods: Eighty-nine patients were initially identified from our databases as having neglect, after thoroughly screening databases, consulting medical practitioners and baseline testing only five met our inclusion criteria and agreed to participate. Sixty-five patients were excluded as they did not meet safety criteria for tDCS (epilepsy, metal implants), suffered from other medical conditions (i.e., heart disease, epilepsy, current psychiatric disorder) or displayed only mild neglect at baseline testing. Five patients with severe chronic hemispatial neglect were enrolled in a double-blind, placebo-controlled treatment program. TDCS or placebo was applied for 20 minutes over the left (cathodal) and right (anodal) posterior parietal cortex at an intensity of 2 mA on five consecutive days. Treatment conditions were separated by a four week wash-out period. Baseline corrected change in performance on the conventional subtests of the Behavioural Inattention Test (BIT) was our primary endpoint. Results: No treatment-related effects were observed for the BIT change scores and performance on individual subtests. Moreover, patients' performance somewhat improved only during the stimulation period (day one vs day five, irrespective of whether it was placebo or tDCS), but not thirty days later, indicating a practice effect. Discussion: The present study does not provide evidence that tDCS to the posterior parietal cortex improves chronic hemispatial neglect. As a result of in- and exclusion health and safety criteria the majority of patients were excluded, which indicates that performing large randomized controlled trials is not feasible in chronic neglect patients.

INTRODUCTION

One of the most debilitating syndromes following stroke is visuospatial neglect (Heilman et al., 1985). Patients suffering from neglect do not attend to, respond to and mostly ignore information on the contralesional side of space (usually ignoring the left side following right hemispheric damage) (Halligan & Marshall, 1991; Robertson, 1999; Vallar et al., & Bolognini, et al., 2014). Several studies indicate that neglect is a predictor of poor functional outcome (Cherney et al., 2001; Nys et al., 2005; Jehkonen et al., 2006; Nijboer et al., 2013; Nijboer et al., 2014). The majority of neglect patients show spontaneous recovery of neglect in the sub-acute stage (10-12 weeks). However, about 40 percent of the patients are still not fully recovered after one year (Karnath et al., 2011; Rengachary et al., 2011; Nijboer et al., 2013).

Starting in the 1970s, many (experimental) attempts have been made to treat hemispatial neglect and they include prism adaptation, optokinetic stimulation, limb activation and eye patching procedures. These techniques have all shown to be effective to some extent (Luaute et al., 2006). Nonetheless, most of these effects are short-lived and/or do not consistently generalize to situations outside the research setting. This makes understanding the underlying mechanisms of neglect in order to better facilitate treatment an important research goal. Several influential models suggest that neglect results from an imbalance between the two hemispheres (Heilman et al., 1985; Kinsbourne, 1974; Kinsbourne, 1987). Both Heilman (1985) and Kinsbourne (1987) proposed that the right and left hemispheres allocate attention to their contralateral side, that is, left hemisphere to the right side and the right hemisphere to the left side of the visual space. Moreover, the right hemisphere is able to direct attention to both sides of the visual space. Kinsbourne (1974) further proposed that attention systems in both hemispheres inhibit each other via transcallossal pathways. A lesion in the right hemisphere will therefore not only result in reduced activity of the attentional system in that hemisphere, but due to loss of transcallosal inhibition by the damaged right hemisphere, will cause over-activation of the attentional system in the left hemisphere as well. Arguably, the lateralized deficits frequently observed in neglect are a direct result of a dominating attentional system in the left hemisphere and therefore a rightward attentional bias. In contrast, the right hemisphere can better compensate for the damaged left hemisphere, since it is proposed to be capable of allocating attention to both sides.

Restoring the interhemispheric balance by modulating brain activity can be achieved through the use of non-invasive brain stimulation (NBIS) techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) (Nitsche et al., 2008; Hesse et al., 2011). Both TMS and tDCS have been explored as a possible means for treating neglect patients. Several studies have demonstrated that TMS can be effective in ameliorating lateralized deficits using both low-frequency rTMS of the contralesional (overactive) hemisphere (Brighina et al., 2003; Shindo et al; 2006; Koch et al., 2008; Song et al., 2009), and high frequency protocols (20 Hz) over the ipsilesional hemisphere (Kim et al., 2010). Although the effects seem promising, most of these studies are proof of principle studies and the number of sufficiently powered randomized controlled trials is still limited (Fasotti and Van Kessel, 2013; Muri et al., 2013). Moreover, it is unknown whether a daily application of TMS is feasible in a clinical setting (Muri et al., 2013).

TDCS is another transcranial stimulation method that can have positive effects on treating neglect by way of simultaneously hypo- and hyperpolarizing cortical tissue by delivering a constant, low intensity current overlying to the sites of interest. TDCS is safe, well tolerated and not associated with serious adverse events (Nitsche et al., 2008). Together with the fact that tDCS devices are portable and relatively cheap, this makes tDCS an attractive method for professionals to use in the clinic or at home. It is generally accepted that tDCS has both short-lasting membrane effects and longer-lasting synaptic effects (see Stagg and Nitsche et al., 2011 for details), and dual stimulation (either facilitatory or inhibitory) fits well into Kinsbourne's model of hemispheric rivalry. However, effects of tDCS in neglect patients have been reported in only few studies (Ko et al., 2008; Sparing et al., 2009; Sunwoo et al., 2013; Brem et al., 2014). Ko and colleagues (2008) studied the consequences of a single 20 minute session of anodal tDCS at 2 mA of the right PPC in fifteen sub-acute stroke patients with spatial neglect, and found improvement on a line bisection test and a cancellation task. Sunwoo and colleagues (2013) also tested the effect of single session tDCS in ten neglect patients but used both anodal stimulation over the right PPC and cathodal stimulation over the left PPC (2.0 mA, 20 minutes), only cathodal over the left PPC and placebo control. They found significant improvements after both dual-mode tDCS and only cathodal tDCS on a line bisection test as opposed to the placebo condition. The effect of dual-mode stimulation was stronger than cathodal tDCS only. Sparing et al (2009) also used dual application of tDCS in a cross-over design with two sessions of tDCS (1.0 mA, 10 minutes) in ten neglect patients and reported improvement on a line bisection test but not on a visual detection task. Thus, using tDCS in a manner consistent with reducing the imbalance in attention allocation has been proven successful to some extent (single session, limited tasks). However, the research on multiple sessions remains relatively scarce. Only one recent single case study has used multiple treatment sessions. Brem et al., (2014) combined dual-mode tDCS with cognitive neglect therapy during treatment of a single patient in the post-acute phase. During the course of four weeks, either cognitive therapy only was given (weeks 1 and 4) or it was combined with either placebo or dual-mode tDCS (week 2) or dual mode tDCS only (week 3). Compared to placebo stimulation, improvements were observed for covert attention to the left side after biparietal tDCS as well as qualitative improvements on line bisection and copying. In the current study we focussed on the effects of multiple sessions of dual stimulation tDCS without concomitant cognitive training in chronic stroke patients. We aimed to study both the feasibility and efficacy of multiple sessions of tDCS in a placebo controlled treatment program. TDCS or placebo 'stimulation' was applied, each for a period of five consecutive days. Similar to previous studies with dual-mode tDCS, we hypothesized that tDCS applied to the left (cathodal) and right (anodal) posterior parietal cortex would improve activity causing a shift in attention and reductions in neglect.

METHODS

Ethics Statement

The ethical institutional review board of the University Medical Centre Utrecht approved this study. All patients gave written informed consent prior to participation and received further information when needed. All study procedures have been conducted according to the principles which are outlined in the Declaration of Helsinki.

Subjects

Patients were recruited via advertisements on social media and from several healthcare institutions, such as 'Stichting zorggroep Noord-West Veluwe', 'Stichting Nieuw Unicum', 'de Hoogstraat Revalidatie' and the University Medical Center in Utrecht, The Netherlands. Inclusion was verified by a tDCS screening questionnaire and was based on the following criteria: (1) left hemispatial neglect after right hemispheric lesion, (2) right-handed, (3) older than the age of 18, (4) more than four months after stroke. Exclusion was based on the following criteria: (1) severe language and communication disorders, (2) bilateral cortical damage, (3) psychiatric disorders, (4) alcohol and/or drug addiction, (5) epilepsy, (6) eczema or damages on the scalp, (7) metal or other foreign parts in the head. We identified 89 patients who exhibited neglect shortly after the stroke. After the thoroughly screening our databases i.e., checking medical background and neglect severity and consulting medical practitioners/docters for stimulation contra-indications, approximately half of the patients had to be excluded and were not further invited. Thereafter about 47 patients were invited by letter, 19 did not respond/did not want to participate. Of these 28 potential candidates only 5 out could be included (see Table 1 for patient demographics and Table 2 for reasons for exclusion. This table contains patients who were excluded after checking the medical background/consultation with medical practitioners as well as the patients who were excluded after sending letters to them. It does not include the 19 patients who did not want to participate). Patients were considered to suffer from neglect when the aggregate score on the conventional tasks was 129 or lower (total range 0-146) on the baseline and/or pre-treatment session (i.e., baseline and the pre-test).

Table 1. *Patient demographics.*

Pt[1]	Gender	Age	Time Post-stroke (Y,M)	Etiology	Lesion location	Mobility[2]	Barthel Index	BIT-C[3]
AB	M	52	(2,4)	Hemorrhage	rP,BG[4]	Impaired	15	136
BO	M	69	(1,0)	Ischemia	rO, TH, CI[5]	Intact	18	111.5
BU	F	65	(1,4)	Hemorrhage	rP	Intact	10	131
VO	F	76	(7,2)	Hemorrhage	rT, C[6]	Impaired	18	56
WE	M	62	(12,4)	Ischemia	rP, T	Impaired	14	71

Patient AB, WE were recruited from social media; BU, BO from the Hoogstraat Revalidatie; VO from Stichting Noord-West Veluwe[1]. Mobility: AB, BO, WE, VO were left hemiplegic, only VO was permanently in a wheelchair[2]; BIT-C= baseline measures on the Conventional Behavioral Inattention Test[3] r = right hemisphere, P= Parietal, BG = Basal Ganglia[4]; O= Occipital, TH = Thalamus, CI = Capsula Interna[5]; T = Temporal; C = Central[6]

Overall, 51 patients were excluded because of criteria specifically related to tDCS (medical conditions, epilepsy, metal implants, eczema, bilateral lesions). Nine patients no longer showed neglect at baseline testing (see Table 2). Four patients were residing in a nursing home where we did not have permission to test the patient. We excluded one patient during the tDCS treatment condition (see table 2; preliminary termination). The patient became emotional, and felt morose. Although we could not establish a causal relation between the patient's emotional state and tDCS, we nonetheless stopped the treatment, since non-invasive brain stimulation of the parietal cortex has been linked to changes in emotional state and mood (Schutter & van Honk, 2005; Schutter et al., 2009).

Table 2. *Primary reason of exclusion for 65 patients who were identified from our databases*

Reason exclusion	Number of patients excluded
Medical conditions*	21
Epilepsy	12
(Metal) implants	11
Bilateral lesions	5
Mild neglect at baseline testing	9
Nursing home **	4
Preliminary termination	1
Eczema	1
Language problems	1
Total Exclusion	65

*Medical conditions included mental retardation, suffering from severe aphasia, tumour, alcohol addiction, COPD, PTSD, depression, delusions, severe heart conditions, pacemaker **We did not have permission to conduct our study at the nursing home where these patients were residing, which is why these patients could not participate.

Study design

Patients were seen 12 times within a 79 days, see Table 3 for the exact timeline. Baseline testing or the screening took place on day 1, then the first condition (either experimental or placebo) started two weeks later. Four weeks later[5], the other condition took place. During both periods, patients performed pre- and post-stimulation assessment daily for 5 consecutive days. Pre- and post-stimulation assessment consisted of conventional BIT tasks (see stimuli task and procedure section).

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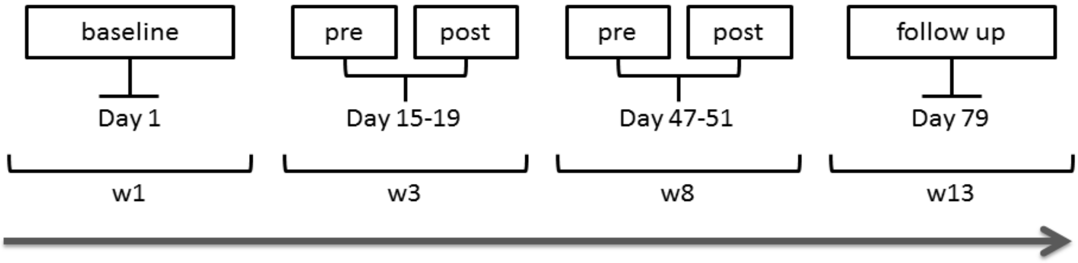
[5] This was however not the case for patient BU because of other illness and treatment. She had a six months interval, instead of four weeks, in between the treatment sessions.

Table 3. *Timeline of the study design. Patients are tested 12 times within a 79 time frame on the BIT-C. Only in week 3 and 8 tDCS was applied in between the pre-post BIT assessment (see text for details).*



Task, Stimuli and Procedure

Patients were treated and tested at home or at the nursing residence. We ensured that all measurements were conducted in a quiet room and that patients were seated as comfortable as possible. All tests were presented directly in front of the subjects' mid-sagittal plane, and stimulus-sheets were fixed to the table in order to prevent movement of the material. The order of tests was randomized between the days, but was the same within one day (pre- and post- assessment). The whole test procedure lasted one hour. In all sessions the six conventional tasks of the Behavioral attention test were administered, consisting of Star Cancellation (SC), Letter Cancellation (LC), Line crossing (LiC) Line Bisection (LB), Figure and shape copying (FSC-A&B) and Representational drawing (RD). We utilized the standard procedure and outcome measures provided by the BIT-Conventional test (see manual BIT for details)[6]. We only administered the conventional subtests of the BIT and not the complete BIT including behavioral subtests). The conventional subtests are usually administered to diagnose the presence or absence of neglect and provides a range (0-146) and a clear cut off score. Additionally, another outcome measure, other than provided by the BIT, was the horizontal Center of Cancellation (CoC). The CoC is an indicative measure of severity of neglect, since it obtains information about the location of cancelled items. Specifically, a positive CoC-score indicates lateralized deficits on the (far) left and vice versa. A CoC-score towards zero means a more symmetrical spatial error distribution. Calculations for the CoC were adapted from Dalmaijer et al., 2014. For the statistical analyses, we derived a composite BIT score (range 0-146) for each measurement (pre-assessment and post assessment), consisting of just one outcome measure. Also, a *clustered* composite score was calculated; the cancellation tests

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[6] Only for the LB we obtained a different procedure. Patients performed this test twice (twice before and after treatment). Outcome measures were the average deviation in mm and were for each separate LB assessment converted into a score provided by the BIT-C (either 0,1,2,3). Thereafter these separate LB assessments were averaged (e.g., average line 1a and 1b; 2a and 2b etc.)

were clustered, as well as the line bisection and the drawing tests, according to norms provided by the BIT-C. Assessment and stimulation lasted approximately one hour.

Transcranial direct-current stimulation (tDCS)

In between the pre- and post-BIT assessments, tDCS or placebo 'stimulation' was applied, in a double blind procedure, for 20 minutes. A battery-driven direct current stimulator (NeuroConn DC-Stimulator; serial number 0096) was used to deliver the electrical current. The stimulation parameters were set at a current of 2000 µA, and a resistance of < 10kOhm. This was applied for 1200 seconds with ramping up in 30 seconds and ramping down in 30 seconds. Electrodes were located over the posterior parietal lobe, corresponding with P3 (left undamaged hemisphere, cathodal electrode) and P4 (right damaged hemisphere, anodal electrode) according to the international 10/20 EEG system (Figure 1). A tight cap was used in order to maximize contact between the scalp and the entire surface of the electrode. In a double-blind procedure the experimenter entered a previously determined code, which referred to either tDCS or placebo. Resistance was monitored during stimulation to ensure that resistance remained lower than 10kOhm. All patients sat in an upright position during tDCS-treatment and tolerated the treatment with tDCS without any adverse side-effects. Most patients reported a slight tingling sensation beneath the right (anodal) electrode at the onset (during the ramping-up) of tDCS. The skin, underneath the electrode, was checked for possible skin burns or abrasion prior to each and after each tDCS application. During placebo condition, 30 seconds of real stimulation at the onset was given. Patients VO, AB and WE received tDCS in the first week, and placebo in the second (see Table 4). This order was reversed for patient BU and BO. Pt. AB was convinced that he received tDCS stimulation the second week, and pt. BU thought the first week, which was in both cases incorrect. Medication was monitored and was kept stable during the treatment weeks.

Table. 4. *Type and order of tDCS stimulation administered and blind check.*

Pt	TDCS	Placebo	Correct
VO	1	2	No*
BU	2	1	No
AB	1	2	No
BO	2	1	No*
WE	1	2	Yes*

* Pt. VO, WE and BO could not disentangle the two treatment weeks but when giving a forced choice. WE was correct and VO and BO were incorrect.

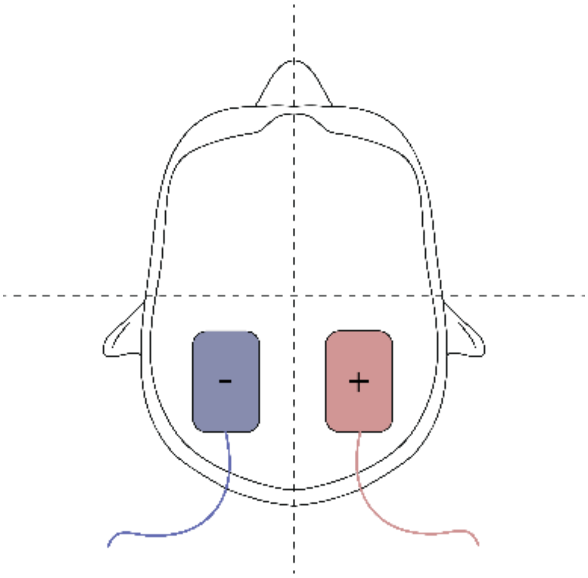

Figure 1. tDCS set up. Red + = anodal electrode (excitatory); Blue - = cathodal electrode (inhibitory).

Data-analyses

For each patient a composite score on the conventional tasks of the BIT was calculated for each day. To recall, the composite score was derived on the summed performance on the SC, LC, LiC, LB, FSC-A, FSC-B, and RD (see Wilson, 1987, for details). For the treatment days (either placebo or tDCS) a baseline corrected difference score was calculated by subtracting the post- from the pre-assessment scores. Note that in the result section day 1 reflects the first treatment day (day 15 in timeline). The real baseline was only used as a screening for the presence of neglect.

Due to the small sample size, normality did not hold and non-parametric tests were performed. To assess immediate effects of tDCS, performance during tDCS vs. placebo conditions was tested with a Wilcoxon signed rank test (Wilcoxon et al., 1945). This analysis was conducted with the average (day 1 till 5) BIT-C pre-post assessment difference score as dependent variable. Similar analyses were performed with clustered BIT-C and the CoC as dependent measures.

Intermediate (difference score day 1 pre-test and day 5 post-test) and follow-up effects (difference score day 1 pre-test and day 30 pre-test) between tDCS and placebo treatment were tested on the *total* BIT-C-composite, the *clustered* BIT-C-composite and the CoC, with a Wilcoxon signed rank test .

In order to assess whether the BIT conventional scores changed over the course of the 5 treatment days as a function of tDCS or placebo 'stimulation', two separate Friedman tests (for the placebo and for the tDCS condition) were conducted with time (day 1 till 5) as within subject factor on both the aggregate BIT score and the CoC of the Star cancellation.

Lastly, in order to test whether individual patients were perhaps differentially sensitive to tDCS treatment, a Wilcoxon signed rank test was conducted for each patient separately. Difference score between pre- and post-assessment (day 1 till 5) was taken as dependent variable and tDCS condition (tDCS vs. placebo) as independent variable. In all non-parametric statistics we reported the Exact Test instead of the Asymptotic Test which is more accurate/conservative with smaller samples (Bellera et al., 2010). Alpha level of significance was set at 0.05 (two-tailed).

RESULTS

Immediate effects of tDCS versus placebo on the BIT Conventional total composite scores

In order to assess the immediate effects of tDCS on performance, the difference between tDCS stimulation and placebo was tested with a related Samples Wilcoxon signed rank test. Dependent measure was the pre-post assessment difference score (averaged over day 1 till 5). As can be seen in Figure 2, there seems a slight difference between treatment and placebo on the average performance, in favour of the placebo condition. However, this did not reach significance (*Z* = -1,483, *p* = .188). Inspection of the individual patient data suggests that this difference was mostly evident in the performance of patient AB, (see Figure 3[7]).

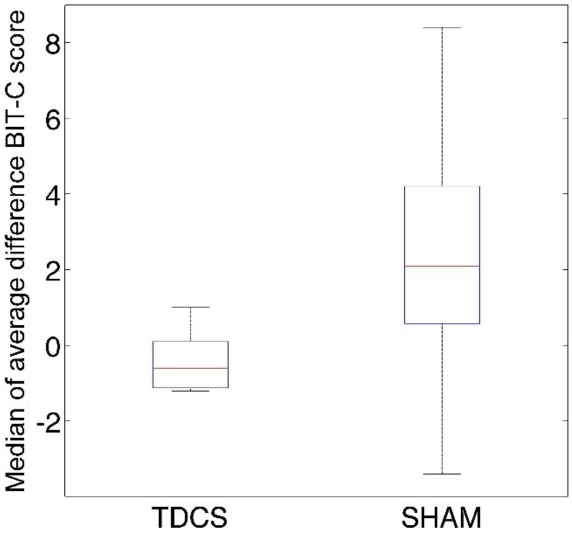

Figure 2. The median of all patients' average difference scores (post- pre) on the BIT-C across five days for the tDCS and placebo condition. A positive value indicates an improvement after treatment. Whiskers represent the most extreme data points. Note that the treatment-weeks were separated by 4 weeks. VO, AB and WE received tDCS stimulation in the first week (in timeline: day 15-19) and BU and BO in the second week (in timeline: day 47-51).

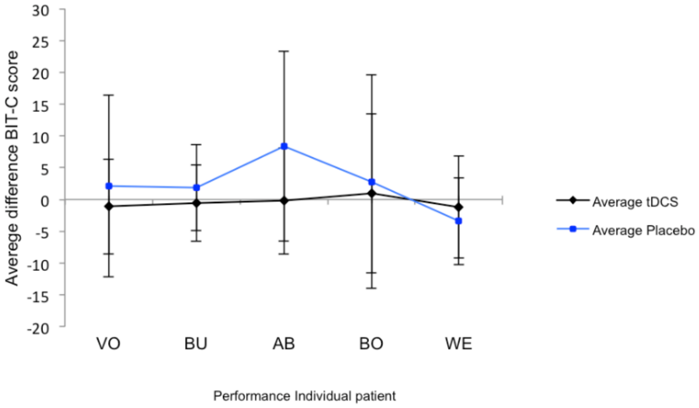

Figure 3. Difference score (post-pre) on the BIT-C, averaged over the different treatment conditions (tDCS vs. placebo) for each individual patient. A positive value indicates an improvement after treatment. Error bars represent standard deviations.

Immediate effects of tDCS treatment on the clustered Composite score

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[7] In figure 3 we present averages instead of the medians, because in the Wilcoxon Rank test these averages were converted into medians.

We divided the overall composite (baseline-corrected difference score) in the clustered composites (cancellation, drawing and line bisection). All three clusters did not differ significantly between treatment and placebo, as can be seen in Table 5.

Table 5. *The median and significance level of all patients' average difference scores (post- pre) on the clusters (cancellation, line bisection, drawing) of the BIT-C across five days for the tDCS and placebo condition. The most extreme data-points are shown in parentheses (lower, upper).*

Test	tDCS	Placebo	Z-statistic	P-Value
Cancellation Test	-.06 (-1.4,0.2)	2.4 (-3.6,7.6)	-1.483	.188
Line Bisection Test	-.4 (-1.3,0.8)	0 (-1,0.9)	-.674	.625
Drawing test	.4 (0,3)	0 (-0.2,0.8)	-.944	.438

Direct effects of tDCS treatment on the Center of Cancellation

Horizontal spatial distribution of the cancelled items (as assessed with the CoC) in the star cancellation did, on average, not differ between treatment conditions (*Z* = -.674, *p* = .625).

Intermediate and follow-up effects of tDCS treatment on the BIT Conventional composite scores

Intermediate and follow-up treatment effects were assessed with a related samples Wilcoxon signed rank test, using the averaged BIT-C-composite difference score. Intermediate performance consisted of a difference score between day 1 pre-test and day 5 post-test. The follow up performance consisted of a difference score between day 1 pre-test and day 30 pre-test. As can be seen in Figure 4, patients' performance, on average, improved from day 1 till day 5 (left panel), hence the positive scores. However, both the intermediate difference score (*Z* = -.944, *p* = .438) and follow-up difference score (*Z* = -1.483, *p* = .188) performances did not differ significantly between tDCS and placebo. Interestingly, a one sample Wilcoxon ranks test against zero revealed a significant effect in the intermediate difference score performance (*Z* = -2.601, *p* = .006) as opposed to the follow-up difference score performance (*Z* = -.816, *p* = .447), indicating an improvement as a function of repeated testing and not as a function of time.

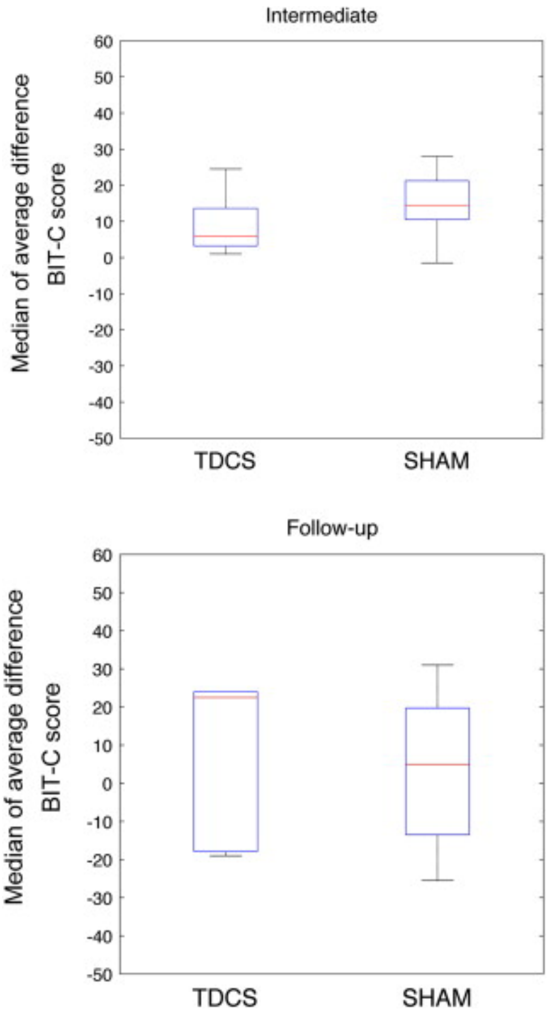

Figure 4. Intermediate (top graph) and follow-up median of the difference (bottom graph) scores (post- pre) on the BIT-C for the different treatment conditions (tDCS vs placebo), see text for details. A positive value indicates an improvement after treatment. Whiskers represent the most extreme data points.

Intermediate and follow-up effects of tDCS treatment on the clustered BIT Conventional composite scores

Visual inspection of the data (see Table 6) suggested an improvement after either treatment for the cancellation tests, hence the positive value. However, tDCS and placebo did not differ significantly from each other. Furthermore, a one sample Wilcoxon ranks test against zero revealed a significant practice effect of only the intermediate performance, for only the Cancellation tests (Z = -2.652, p = .006), but not for other clusters (Z < -1.125, p > .283), indicating that the aforementioned effects of repeated testing were mainly driven by performance on the Cancellation tests.

Table 6. *Median average difference 'intermediate' and 'follow-up' scores and significance level for the clustered BIT-Conventional tests. The most extreme data-points are shown in parentheses (lower, upper).*

Test	TDCS	Placebo	Z-statistic	P-Value
Cancellation Test				
Intermediate	5 (2,21)	15 (-2,28)	-.944	.438
Follow-up	30 (-20,23)	2 (-22,34)	-.135	1.000
Line Bisection Test				
Intermediate	0 (-1.5,1)	-0.5 (-2.5,2)	-.271	.875
Follow-up	0.5 (-1.2.5)	-1.5 (-4,4)	-.948	.375
Drawing Tests				
Intermediate	-3 (-5,1)	1 (-1,2)	-1.761	.125
Follow up	0 (-2,3)	-1 (-2,3)	-.756	.625

Intermediate and Follow up effects of tDCS treatment on the Center of Cancellation

Horizontal spatial distribution of the cancelled items (as assessed with the CoC) in the star cancellation did not differ between treatment conditions in the intermediate condition (Z = -.674, p = .625), but showed a marginally significant effect in the follow-up condition (Z = -.2023, p = .063), indicating that the median of the average difference score between day 1-30 was smaller for tDCS (median: .006) than placebo (median -.646), suggesting a more symmetrical spatial error distribution after tDCS treatment, as opposed to placebo.

Short-term effects of tDCS over the five treatment days on the conventional composite BIT scores.

As can be seen in Figure 5, the overall composite *difference* score (i.e., difference between post-pre-assessment) fluctuated over time (e.g., a positive score indicates an improvement after either tDCS or placebo treatment). Generally, these fluctuations were more pronounced in the placebo-week as opposed to the week with tDCS and they were mostly visible in the data of patients AB, BO and VO. The Friedman test on time (day 1, day 2, day 3, day 4, day, day 5) showed that the overall composite score was not affected by time in the tDCS treatment condition ($\chi2$ (4) = .687, p = .965), nor in the placebo condition ($\chi2$ (4) = 2.880, p = .613.

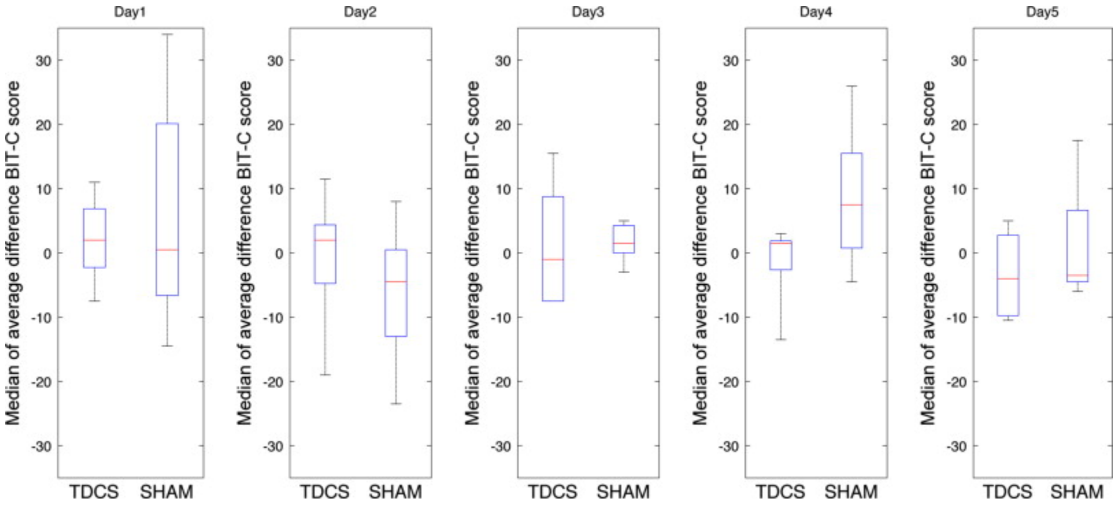

Figure 5. The median of the averaged difference score (post- minus pre-assessment) on the BIT-C for the different treatment conditions (tDCS vs placebo) over the 5 treatment days. A positive value indicates an improvement after treatment. Whiskers represent the most extreme data points.

Short-term effects of tDCS treatment on the Center of Cancellation

No effects of day in the tDCS treatment condition (χ2 (4) = 6.240, *p* = .183) and placebo condition (χ2 (4) = 7.360, *p* = .118) on the horizontal spatial distribution of the cancelled items (as assessed with the CoC) in the star cancellation (see Figure 6).

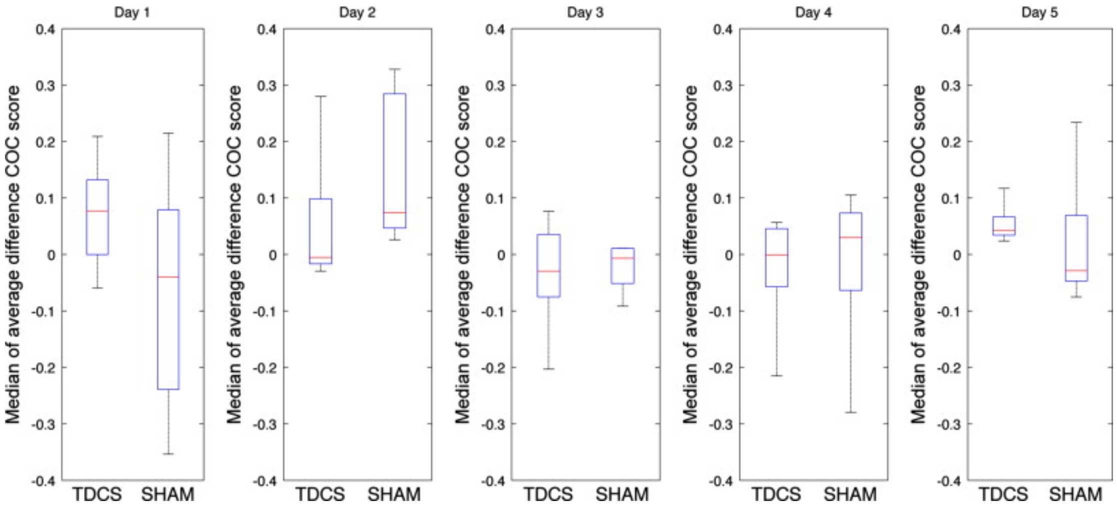

Figure 6. The median of average difference Score of the Center of Cancellation of the Star Cancellation. A positive difference CoC-score represents a shift to the right (indicating lateralized deficits on the (far) left) and vice versa. A CoC-score towards zero means a more symmetrical spatial error distribution. Whiskers represent the most extreme data points.

Individual differences between tDCS and placebo

Lastly, in order to test whether individual patients were perhaps differentially sensitive to tDCS treatment, a Wilcoxon signed rank test between tDCS and placebo was conducted for each patient separately. Again, as can be seen in Figure 7, the difference in treatment was mostly evident, albeit not significant, in patient AB (See Table 7).

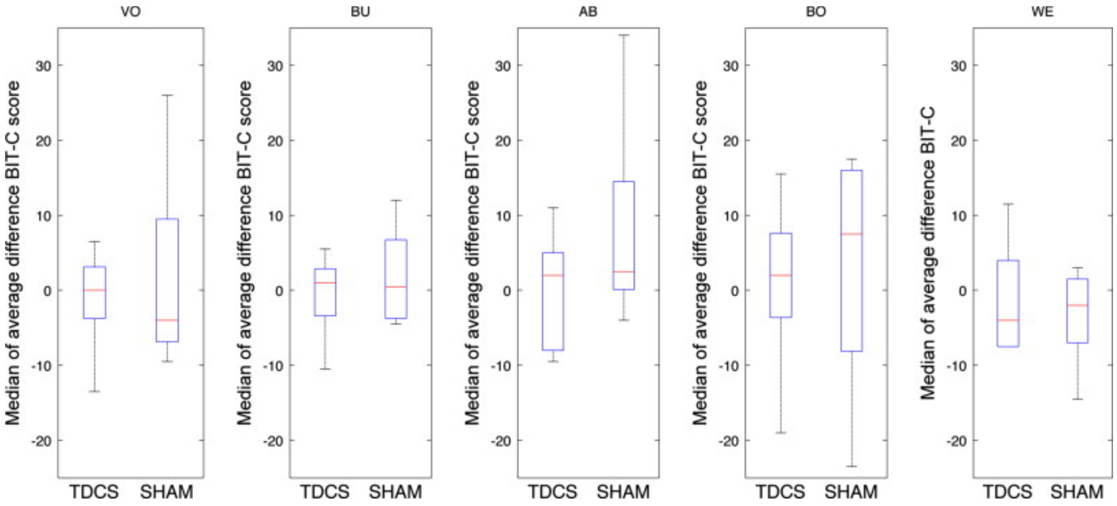

Figure 7. The median of the averaged difference scores and significance level for the BIT-Conventional tests for each individual patient. Whiskers represent the most extreme data points.

Table 7. *Z-statistic and significance level for the BIT-Conventional tests for each individual patient.*

Pt	Z-statistic	P-Value
VO	-.674	.625
BU	-.944	.438
AB	-1.753	.125
BO	-.405	.813
WE	-.271	.875

DISCUSSION

The aim of the current study was to evaluate the feasibility and both short-term and long-term effects of multiple sessions of tDCS on hemispatial neglect. We hypothesized that tDCS would rebalance the attention systems in the left and right hemisphere, and, as a result, would enhance attentional processing in the contralesional hemispace in order to reduce lateralized deficits. We used the conventional subtests of the BIT to assess the effects of multiple and daily applications of biparietal tDCS.

Analyses of the BIT-Conventional composite scores did not reveal a significant tDCS treatment effect on performance. More specifically, there was neither an effect on the deviation from the actual centre on the line-bisection, nor in the number of cancellations, or a shift in location of these cancellations after tDCS as compared to placebo ‘stimulation’. There was however an improvement during treatment. More specifically, patients’ performance somewhat improved in the cancellation tasks in both the placebo and tDCS treatment weeks (day one vs day five), but not thirty days later, indicating a practice effect. This finding indicates that learning effects due to repeated testing can confound or possibly even explain improvements in neglect especially in open-label studies and studies without proper control conditions.

Unlike the recent promise of single session tDCS (Ko et al 2008; Sparing et al 2009; Sunwoo et al., 2014) and multiple session tDCS in a single patient (Brem et al., 2014), no robust amelioration of lateralization deficits across clinical measures were found in our patients. It should be noted however, that Sparing and colleagues (2009), only found improvement on a line bisection task, and not on visual search. Generally, most effects were found on the line bisection in the previous studies. Interestingly, we did not find such an effect across multiple sessions. One could speculate that a lack of statistical power could be the main cause of our lack of results, since we had only five participants. However, one other study did find effects of tDCS in only a single patient (Brem et al., 2014). Individual trends were not present in our data. However, considering the large variation in our data, we cannot rule out a statistical power issue here. Another important difference with previous studies is that all studies, but one (Sunwoo et al., 2013), assessed and stimulated the patients in the sub-acute stage (< six months post-stroke), and we performed our measurements in the chronic stage. As a result of the inclusion of chronic patients there may have been less room for neurological improvement indicating that patients might have reached a plateau level in recovery. However when including patients in the sub-acute stage, tDCS could have facilitated neurological recovery, as the brain is especially sensitive to neurological reorganization during the first 3 months post-stroke (Robertson & Murre, 1999; Murphy and Corbett, 2009; Kwakkel et al., 2004; Nijboer et al., 2013).

To the best of our knowledge, only Brem et al., (2014) applied more than 10 sessions in a single case study. The other studies (Ko et al., 2008; Sparing et al., 2009; Sunwoo et al., 2014) showing positive results administered less tDCS sessions than we did. Five sessions of tDCS applied in the chronic stage might nonetheless be insufficient to induce reliable changes and could be one of the reasons we did not find a difference between tDCS and placebo. Moreover, it has recently been observed that, following neurostimulation, the sensorimotor cortex reorganizes differently in chronic and subacute stroke patients, suggesting that these stages reflect different mechanisms of neuroplasticity (Yarossi et al., 2014) and may require different stimulation parameters. Furthermore, although tDCS as a monotherapy has been shown effective before (Ko et al., 2008; Sparing et al., 2009; Sunwoo et al., 2014), the functional networks recruited might be too diffuse, especially when tests are administered offline. If tDCS is implemented as an adjuvant therapy, next to scanning training or prism adaptation for instance, it might recruit the attentional networks necessary for improving neglect. Several authors studying rehabilitation for motor (Bologinini et al., 2009; Miniussi & Vallar, 2011; Sandrini & Cohen, 2013) and language problems (de Aguiar et al., 2014) have recently stressed the importance of combining a behavioural intervention with non-invasive brain stimulation.

In recent studies, the effect of tDCS has been questioned (Horvath et al., 2014; Horvath et al., 2015). In a systematic review, the authors evaluated the effectiveness of tDCS in literature (Horvath et al., 2015). Instead of including studies with behavioral outcome measures, they included studies utilizing neurophysiological outcome measures in mostly healthy subjects, such as motor evoked potentials (MEP) combined with TMS, event related potentials (ERP's), EEG and fMRI. Reliable effects were found only on corticospinal excitability as measured with MEP. They concluded that tDCS could not reliably induce a physiological effect in healthy subjects, and of all the aforementioned measures motor evoked potentials were the most sensitive to tDCS. However it should be noted that the number of available studies included in the meta-analyses for the different neurophysiological outcomes, except for the MEP, was very limited, which makes it difficult to draw definite conclusions. The results indicate that the neurophysiological effects of tDCS are difficult to quantify. How do we interpret these findings in light of behavioral findings? In another study, Horvath et al. (2014) further stated eminent indicators that could cause variability between subjects and inconsistencies in effectiveness, both neurophysiological and behaviorally. Yet, a recent review shows that tDCS has reliable behavioral effects in healthy volunteers (for a review see Coffman et al 2014). The observed variability in efficacy are most likely due to individuals' unique anatomy, skull thickness, subcutaneous fat levels, cerebrospinal fluid density, scalp to cortex distance and other factors that determine the flow of current and how much electricity reaches the cortical surface (Stagg & Nitsche, 2011). In addition, the effects also depend on differences in physiological susceptibility to exogenous electric currents of the brain itself. Although we have no anatomical information about our included patients, individual variability could explain some of our null-findings, that is, despite placing the electrodes in a standardized way, individual variability in the above factors and additionally in lesion characteristics, may have precluded any behavioral effects.

In terms of the feasibility of conducting randomized controlled trials involving multiple consecutive sessions of tDCS, patients tolerate the daily applications well. Most reported sensations were underneath the anode electrode at the onset of the stimulation, the ramping up phase, in both the tDCS and placebo condition. Although skin burns underneath the electrodes have been reported in repeated applications on the same scalp locations (Loo et al., 2010; Frank et., al 2010; Palm et al., 2008), our patients did not show any physical aversive effects during and after treatment. When the resistance exceeded levels of 10kOhm, a small amount of conduction gel was added or the site of the electrodes was massaged gently. One patient showed dryness of skin underneath the stimulated area, and we used a lubricant after the stimulation session to prevent skin damage.

Apart from the lack of efficacy, another important issue which hampers evaluation of tDCS in our study was our large number of a priori excluded patients. Most patients were excluded on the bases of unstable medical conditions. Medical conditions in our sample included mental retardation, epilepsy, suffering from severe aphasia, tumour, alcohol and or drug addiction, COPD, PTSD, delusions, and severe heart conditions. Generally, there is little information available about the exact in- and exclusion criteria for stimulation techniques in stroke patients. Nitsche et al. (2008) state that patients should be excluded when displaying an unstable medical history, but what does that mean? Unstable in the sense of psychological problems or neurological problems, and to what extent? Also, tDCS has not directly been associated with an increased risk of epilepsy in healthy individuals, but literature is not sure what might happen when applying dual tDCS, especially with the anode electrode, in epileptic vulnerable people (Nitsche et al., 2008). We therefore also excluded patients whom did not have epilepsy themselves, but with family records of epilepsy. Perhaps this has been somewhat too conservative. So far, there have only been a few studies investigating tDCS in neglect. This might reflect the difficulties in studying this set-up in this patient population and the relative small sample sizes, which ranged from a single case to fifteen patients. Unfortunately however, the number of excluded patients prior to treatment is usually not reported. It is particularly interesting to note that other studies with stroke patients with language problems (see for a review Aguiar et al., 2015) or motor problems (for a review see Flöel, 2014) usually have larger samples. Unfortunately, again, the number of patients that has been excluded a priori is usually not reported. However, it may be that since chronic hemispatial neglect is often associated with more comorbidity, this hampers research with stimulation techniques and possible routine clinical application, to a larger extent than other post-stroke cognitive problems. This again underscores the fact that displaying neglect after stroke is not only a predictor of poor functional outcome, it is also very difficult to treat.

In conclusion, the present study does not provide evidence that tDCS to the posterior parietal cortex improves hemispatial neglect in severe chronic neglect patients. Due to the strict in- and exclusion health and safety criteria the majority of patients were excluded and this suggests that performing large randomized controlled trials is not feasible in chronic neglect patients.

ACKNOWLEDGMENTS

The authors would like to thank all the subjects for participation and N. de Jonge and I.A. Bos for their help with data acquisition.

Chapter 9

General Discussion

Miranda Smit

GENERAL DISCUSSION

In the previous chapters I discussed how and to what extent primary sensory input can influence higher order representations of the body and space. In the first part I mainly focused on body and space related interactions in healthy individuals, in the second part I focused on these interactions in patients with acquired brain damage.

1. BODY AND SPACE RELATED INTERACTIONS IN HEALTHY INDIVIDUALS

More specifically, in the first part I gained basic understanding of whether hand ownership is differentially experienced in the left and right hand. I further wanted to know whether handedness had a differential impact on the ownership experience. In other words, is body ownership lateralized?

In chapter 2 I aimed to test whether experiences such as subjective feeling of ownership shift and proprioceptive drift, as assessed with the RHI, are differentiated by handedness and differed between the left and right hand. Sinistrals, dextrals, and mixed handed individuals were submitted to the RHI. In summary, the results (both on the embodiment questionnaire and proprioceptive drift) present a similar experience of ownership for all groups. Although previous (small groups) research has shown differences between sinistrals, dextrals, and mixed handed individuals which was linked to interhemispheric connectivity (Christman et al., 2008; Prichard et al., 2013; Gutwinski et al., 2011), the results in chapter 2 showed no lateralization effects of visuotactile integration and body ownership. I suggest, based on my own study with relatively large groups, that body ownership may not be as lateralized as current literature indicates.

In addition, I also found it did not matter in terms of outcome measures whether the illusion was applied to the left or the right hand. This is particularly noteworthy since previous research linked body ownership to the right hemisphere. These findings are consistent with findings of a study that was published while the current research was conducted (Bertamini & O'Sullivan, 2014). They found no difference in proprioceptive drift and embodiment questions for the left and right hand in a group of dextrals. This suggests that hand ownership might be similarly represented in the brain for the left and right hand during the rubber hand illusion.

In chapter 3 I took it a step further and addressed whether actual tactile input was necessary to experience hand ownership. Ferri et al., (2013), found that sense of ownership was evident by mere expectation of touch. To recall, I aimed to investigate this finding by studying whether the mere potential for touch yields a sense of ownership similar in magnitude to that resulting from actually being touched. Two experiments were conducted. The results indicate that *approaching* the rubber hand yields a result similar to that of asynchronous stimulation. Participants experience most ownership over the rubber hand in the 'classic' synchronous condition, followed by the visual only condition. In addition, tactile expectation is able to induce embodiment over a foreign hand, similar in magnitude as actual touch, but *only* when the own hand is placed along the path of the approaching stimulus. This concurs with previous findings (Ferri et al., 2013; Ferri et al., 2017) and suggestions (Ferri and Costantini, 2016) and indicates that our brain uses bottom–up multisensory information, as well as top-down predictions about anticipated sensory input to represent our body or induce changes in the representation of our body (however see Guterstam, Larsson, Zeberg & Ehrsson, 2019, for a different view on this).

In the next chapter (chapter 4) I investigated whether the perceived position of a stimulus in space (a vertical line) could be modulated by changes in perceived body ownership. Previous research has implied a close relationship between the two (Grivaz, 2017). Sixty-five participants administered a landmark task *before* and *after* the RHI. Participants were divided in two groups; receiving either synchronous or the asynchronous stroking in a rubber hand illusion set-up. To recall, in the landmark task, participants had to determine whether a landmark was left or right from the center of a large horizontal screen. Only for the synchronous stroking group, results showed a shift in space to the right (e.g., away from the own arm). These results might suggest that the relevant action space becomes linked to the fake hand and not the real hand. It is worth mentioning that the subjective experience of the illusion did not correlate with this shift in space, however proprioceptive drift did. This might imply that multisensory integration of bodily information drives this shift in PPS and not feelings of ownership per se.

As we have read in previous chapters, the representation of our hands is highly distorted, i.e., short fingers and broad width of the hand. In chapter 5, I investigated how we perceived our hands under different sensory circumstances. Specifically, I tested in 23 individuals whether their perceived hand representation could be differentially modulated by different sensory signals (proprioception, touch, movement). We manipulated the sensory signals in four different conditions in an adapted version of the body localization task: a proprioceptive condition (hand still under monitor), a touch condition (i.e., touch on finger), a movement condition (i.e., movement of finger), and an imagine condition (i.e., absence of the hand).

Results replicate previous findings such as an overestimation of width and an underestimation of length. The overall shape of the hand was perceived wider than it is long. This shape was consistent for all conditions, however when the finger moved, perceived distortions became slightly more apparent. These results therefore suggest that this unconscious representation of our body relies on a stored body-model, which seems unaffected by different sensory input.

Interim conclusion/discussion chapter 2-5

Chapter 2-5 increased our understanding of the body representation in healthy individuals, more specifically these chapters offer us insight whether modulations of primary (multi)sensory input influence higher order body and space representations in healthy individuals. Firstly, no hand lateralization effect was found, neither did it matter whether the illusion was applied to the left or the right hand. I therefore believe that feelings of body ownership may not be as lateralized as current literature indicates and that hand representations in the brain might be equal for the left and right hand during the rubber hand illusion. Next, results indicated that actual touch to induce ownership over a fake hand was not necessary. I therefore suggest that our brain uses bottom–up multisensory information, as well as top-down predictions about anticipated sensory input to represent our hand. I furthermore showed that synchronous multisensory stimulation as opposed to asynchronous stimulation is able to shift the perceived action space towards the fake hand. Critically, the subjective experience of the illusion did not correlate with this shift in space, however proprioceptive drift did. Thus, it seems likely that multisensory integration of bodily information drives this shift in PPS and not feelings of ownership per se. Lastly, results showed that we perceive our hands as highly distorted; an overestimation of width and an underestimation of length. The overall shape of the hand was perceived wider than it is long. What was surprising is that this shape was robust to most sensory modulations (i.e., proprioceptive, tactile and no input). However, when the finger moved, perceived distortions became slightly more apparent. Overall, I conclude that implicit representation of our hand relies on a stored body-model, which seems unaffected by the modulation of sensory input.

2. BODY AND SPACE RELATED INTERACTIONS IN PATIENTS

Research shows that the somatosensory system plays an important role in both body representation (BR) and PPS. The study in chapter 6 aimed to examine the effect of long-term somatosensory loss in the hand on the metric features of the BR, by including patients with somatosensory loss due to stroke and healthy age-matched controls. Two types of representations were examined in both hands; a visual, explicit BR and a somatosensory, implicit BR. Results for the body localization task showed that both patients and controls show the classical distortions; short, wide hands. A few patients experienced a disproportionally large hand. This finding seems to be linked to diminished body awareness, and sensorimotor deficits. With respect to the more conscious body perception, as measured with the template matching task results showed that in general most patient had a veridical percept of their hand. Surprisingly, patients in the severe group perceived the overall shape as to be longer than it is wide (opposite to the somatosensory representation). I attribute this finding to the process of visual-tactile compensation mechanism. Taken together, I conclude patients with moderate to severe sensory impairments still have access to a multimodal representation when somatosensory processing is disturbed.

In chapter 7, I investigated a patient who suffered from complete body disownership after damage to the right temporo-parietal cortex. This patient was unable to recognize, feel or experience his body as his own, despite the fact that he knows it is his own. Although these experiences affected his whole body, problems were most pronounced in both hands, left more than right, and while driving a car: “As if I am in a shell, a passenger whilst driving myself.” There were no problems in motor planning nor motor execution. Further neuropsychological testing showed, despite intact primary visual and somatosensory senses, selective bilateral ownership problems. Previous studies have found that after acquired brain injury and subsequent sensorimotor deficits, individuals were more susceptible for the RHI with their affected hand (Van Stralen et al. 2013, Burin et al, 2015, Zeller et al. 2011, White et al. 2017; Llorens 2017). However, the patient did not experience deficits in the primary senses. It seems that the patient did not benefit from multisensory stimulation; the illusion was most pronounced during visual exposure and he did not differentiate between synchronous and asynchronous stimulation, indicating that he relies more on what he sees rather than the combination of what he sees and feels, suggesting suboptimal multisensory integration. Exercises involving visual input about the body from a third person perspective (i.e., through a mirror) combined with tactile stimulation seem to improve his body awareness.

In chapter 8 I investigated a stimulation technique in order to treat hemispatial neglect. Previous research suggests that we can restore cortical interhemispheric balance by dampening neural activity of the intact hemisphere, combined with increasing neural activity in the damaged hemisphere. This might then reduce hemispatial neglect. In this study, I repeatedly applied transcranial direct current stimulation (tDCS), to the posterior parietal cortex in a polarity dependent fashion to find evidence for improvements in severe hemispatial neglect in chronic patients. We identified eighty-nine patients suffering from neglect from our databases. After multiple screening sessions (e.g., consulting medical practitioners and baseline testing) only five patients were included. A substantial number of patients had to be excluded (65 patients) because they did not meet safety criteria for brain stimulation (epilepsy, metal implants), they suffered from other medical conditions (i.e., heart disease, epilepsy, current psychiatric disorder) or baseline testing did not reveal any neglect. The 5 patients that were included were enrolled in a double-blind, placebo-controlled treatment program. Blinded stimulation (i.e., tDCS or placebo) was applied for 20 minutes for 5 consecutive days. The left (cathodal) electrode and right (anodal) electrode was placed at the posterior parietal cortex at an intensity of 2 mA. Treatment conditions (tDCS or sham stimulation) were separated by a four-week wash-out period. Our primary endpoint was baseline corrected change in performance on the conventional subtests of the Behavioural Inattention Test (BIT). Results showed no treatment-related effects. Patients' performance somewhat did improve only during the stimulation period (day one vs day five, irrespective of whether it was placebo or tDCS), but not at follow up, indicating a practice effect. The present study does not provide evidence that tDCS to the posterior parietal cortex improves chronic hemispatial neglect. As a result of health and safety criteria the majority of patients were excluded. This raises an important issue, that is, performing large randomized controlled trials is difficult to achieve in these patients. A recent trial in the UK raised similar concerns and concluded poor feasibility of sustained application of tDCS, either with or without behavioral training (Learmonth et al., 2021).

Interim discussion chapter 6-8

Chapter 6-8 increased our understanding of the body and space representation in patients with acquired brain damage. Firstly, I found that patients with somatosensory deficits perceive their hand as (normally) distorted as healthy individuals do; wide short hands. A few patients perceived their affected hand as disproportionally large, which I believe is linked to diminished body awareness, and sensorimotor deficits. As expected, most patients had a veridical percept of their conscious hand as assessed with the template matching task. What I found surprising was that patients in the severe group perceived the overall shape as less veridical than patients who are moderately affected and healthy controls. In fact, as opposed to the somatosensory representation, they perceived the overall shape to be longer than wide. I suggest that this is a result of a visual-tactile remapping process; a visual correction of the distorted cortical somatosensory representation, however, this correction becomes redundant when somatosensory information is absent since there is nothing to rescale. Next, I found that a patient *without* primary somatosensory (and visual) deficits still can disown his body. I believe that there was an overreliance on visual input instead of combining visual and somatosensory input, indicating suboptimal multisensory integration. Additionally, I found that exercises that encompasses visual input about the body from a third person perspective (i.e., through a mirror) combined with tactile stimulation improved his body awareness. Finally, treating patients visuospatial neglect repeatedly with tDCS did not improve their behavioral lateralized deficits. Health and safety issues are paramount in this trial and I suggest that with the current parameters performing large randomized controlled trials are difficult to achieve.

Theoretical implications and future directions

What can the aforementioned findings tell us about models of body representation and space representation in healthy individuals and clinical groups? One can conclude from the previous studies that there is a complex interaction between somatosensory input, multisensory integration, body ownership and space representations. Relationship between these processes is sometimes apparent, but other times is not. The challenge is how to define the precise relation between them: For example, metric relations seem not dependent on immediate sensory signals, but rather reliant on a stored representation of our limbs.

A sense of ownership over our limbs does not necessarily depend on somatosensory input, but appears to depend on either multisensory integration and/or visuotactile prediction. This might have implications for certain patient groups who feel less ownership, for example because of suboptimal integration. If body ownership can be modulated by top-down predictions, then these groups can benefit from this top-down mechanism in reinstating limb ownership. Additionally, the modulation of type of touch could also be promising as a possible treatment for reducing body ownership problems since different kinds of touch can modulate the rubber hand illusion, and consequently influence hand ownership. Evidence suggests that affective, tactile input can modulate the subjective experience of the illusion in measures such as proprioceptive drift (van Stralen et al., 2014) and subjective experience of ownership (Crucianelli, Metcalf, Fotopoulou, & Jenkinson, 2013). Affective touch can be described as slow touch (1-10 cm/s), and typically C-fibers, next to Aβ-fibers, will respond. Discriminative or non-affective touch is usually assessed by much faster (30cm/s) stroking which will only activate the Aβ-fibers. A network of brain areas is differentially involved with each type of touch. Generally, discriminative touch is linked to the primary somatosensory cortex and affective touch is linked to the posterior insula. Interestingly, the posterior region of the insula has been linked to body awareness (Baier and Karnath, 2008, Tsakiris et al., 2007, Tsakiris, 2010, Tsakiris et al., 2011). This is of particular interest when normal touch is absent or lessened due to damage to the parietal regions. For body ownership, multisensory integration might be weakened, that is, discriminative touch 'channels' are usually affected in this group and as a consequence patients receive less tactile and proprioceptive input, as a consequence more weight will be given to visual input. The visual capture of the rubber hand in combination with a weaker sense of self, results in a larger rubber hand illusion as has been shown in previous studies (Burin et al., 2015; Smit et al., 2019). Affective touch might, by stimulating the alternative route, reinstate a sense of touch (and therefore a sense of self), which was previously lost or lessened (Jenkinson, Papadaki, Besharati, Moro, Gobbetto et al., 2020). We presented this idea in chapter 7 (Smit, Van Stralen, Van den Munckhof, Snijders & Dijkerman, 2019). Although this patient did not have somatosensory deficits, he did experience diminished ownership over his entire body following a parietotemporal tumor resection, which seem to stem from suboptimal multisensory integration, i.e., an overreliance on visual input. Affective touch did increase feelings of ownership, which was reflected in similar pattern of results as healthy controls in the rubber hand illusion. In short, the differential role of touch and bottom-up sensory integration needs further attention, given promising preliminary results future research could focus on modulation of touch by either bottom up affective touch, and/or top down predictive mechanisms.

CONCLUSION

All in all, the results of this thesis add to our understanding of body perception, multisensory representations, space perception and the complex interaction between. These studies aimed to increase our understanding of hand and space representations in healthy individuals and in individuals with acquired brain damage. We learned that not only visuotactile integration, but also visuotactile prediction can induce a sense of ownership over a foreign object and that providing a combination of 3rd person perspective and touch can reduce body disownership in a patient. Also, multisensory integration of bodily information can change the perceived peripersonal space. We further found that how we perceive our hand seemed to be overall similar for healthy individuals and for individuals with somatosensory deficits following acquired brain damage. Overall, these findings provide further insight into the complex interplay between somatosensory processing, perceived body size and ownership and space perception and as such are consistent with models such as the body matrix (Moseley et al., 2012; Riva, 2018). The challenge for future studies is to define how the different components interact and what the underlying mechanisms are.

Dutch summary

De afgelopen jaren heb ik meer stilgestaan bij hoe schijnbaar eenvoudige handelingen, zoals een kopje koffie in de ochtend pakken, afhankelijk zijn van veel processen die we vaak als vanzelfsprekend beschouwen. Ik moet bijvoorbeeld de locatie van mijn hand, de locatie van de kop koffie, de lengte en breedte van mijn hand en ook hoe ver deze in de ruimte is, 'weten'. Bovendien bestaat de kans dat ik mijn hand moet terugtrekken omdat de beker nog te heet is om aan te raken. We zijn ons er meestal niet van bewust dat we deze handelingen uitvoeren, laat staan dat we ons bewust zijn van het gegeven dat het lichaam dat deze handelingen uitvoert eigenlijk van ons is. We leren lichaamsfuncties vaak waarderen wanneer we iets niet meer kunnen, bijvoorbeeld wanneer we niet weten hoe ver we moeten reiken, wanneer we geen voelbare feedback krijgen wanneer de beker nog te heet is om aan te raken en brandplekken achterlaat, of wanneer de hand vreemd aanvoelt wanneer we naar die beker reiken. In dit proefschrift heb ik processen behandeld die te maken hebben met de representatie van het lichaam en de lichaamsruimte bij zowel gezonde individuen als individuen die een beroerte gehad hebben.

Het somatosensorische systeem: zintuiglijke waarneming.

Het vermogen om aanraking te voelen omvat een complex netwerk dat het somatosensorische systeem wordt genoemd (Franzen, Johansson & Terenius, 1996). We hebben gespecialiseerde receptoren voor de sensaties die we voelen. Als ik terugga naar het vorige voorbeeld waar ik een kopje koffie zou willen pakken, dan zullen de proprioceptoren van mijn lichaam informatie geven over de spierlengte en spierspanning zodat mijn lichaam de positie van mijn hand ten opzichte van de beker (en andere lichaamsdelen en voorwerpen) kan inschatten. Bij het aanraken van de beker of het grijpen naar de beker, reist informatie van deze verschillende receptoren/cellen in mijn huid, spieren en gewrichten naar mijn hersenen via verschillende paden: de spinothalamische route en de mediale lemniscale route. De eerste route verwerkt nociceptieve, thermoceptieve en affectieve informatie, terwijl de laatste route elementaire aanrakingsinformatie van mechanoreceptoren (d.w.z. druk, textuur, trillingen) en proprioceptieve informatie verwerkt. In mijn proefschrift zal ik me voornamelijk concentreren op informatie die door dit mediale lemniscale kanaal reist, dat projecteert via de contralaterale thalamus naar de primaire somatosensorische cortex.

Hogere orde processen die iets zeggen over de grootte en vorm van ons lichaam

Hoe we somatosensorische basissensaties verwerken om hogere orde lichaamspercepties en representaties te bereiken is complex, wanneer het de waargenomen vorm van het lichaam of een lichaamsdeel betreft. In de volgende sectie zal ik bespreken hoe we de lichaamsvorm (met name de handvorm), structuur en afmetingen waarnemen en hoe we efficiënte en succesvolle interacties met de buitenwereld bereiken (haptische verkenning in de peripersoonlijke ruimte). Interessant is dat er aanzienlijk bewijs is dat vervormingen op het niveau in de primaire somatosensorische cortex ook de perceptie van lichaamsgrootte en -vorm beïnvloeden.

Talrijke onderzoeken bij gezonde personen hebben aangetoond dat we ons lichaam als sterk vervormd ervaren (Linkenauger, Kirby, McCulloch & Longo, 2017). Onze hand wordt bijvoorbeeld gezien als breed en kort (Longo & Haggard 2010, Longo et al., 2012; Longo et al., 2015; Saulton et al., 2015; Saulton et al., 2016, Coelho et al., 2016). Het patroon van vervorming komt overeen met de geometrie van het receptieve veld aan de bovenzijde van de hand. Deze receptieve velden zijn ovaal van vorm (Powell en Mountcastle, 1959; Brown et al., 1975), vandaar dat er mediolateraal (vanuit het midden naar de zijkant) meer receptieve veldgrenzen zijn dan proximo-distaal (vanuit het midden naar buiten/de vingers), en daarom nemen we de algemene vorm van de hand breder waar dan dat hij lang is. Dus de tactiele waarneming weerspiegelt de vervormde kenmerken in primaire somatosensorische hersenschors. Dit is echter niet het hele verhaal, aangezien de perceptuele vervormingen niet volledig overeenkomen met de corticale vergroting in de primaire somatosensorische hersenschors zoals blijkt uit de Weber-illusie. Dit geeft aan dat de hersenen op de een of andere manier proberen om de tactiele grootte constant te houden door de primaire, vervormde representatie van het lichaamsoppervlak te herschalen (Taylor-Clarke, Kennet & Haggard 2002). Longo et al., (2010) stellen dat deze tactiele constantheid een product is van het verwijzen naar een hogere vorm van representatie, zoals het opgeslagen lichaamsmodel. Volgens Longo 'kent' dit lichaamsmodel de metrische eigenschappen van het lichaam. Bewijs voor het feit dat de waarneming van ons lichaam afkomstig is van zowel primaire zintuiglijke informatie als informatie van hogere orde, komt voort uit onderzoeken waarin verschillende illusies tactiele afstandswaarneming op een top-down manier mediëren (Taylor-Clarke et al. (2002), de Vignemont, Ehrsson en Haggard (2005), Tajadura-Jiménez et al., (2012), Longo en Sadibolova (2013)). In al deze onderzoeken werd somatosensorische verwerking (en afstandsperceptie) beïnvloed door visuele ervaring. Dezelfde logica geldt voor ons positiegevoel/proprioceptie, dat is het vermogen om de ruimtelijke locatie van onze ledematen te kennen. Signalen afkomstig uit het lichaam (afferente signalen) zijn betrokken bij het verstrekken van proprioceptieve informatie. Echter, directe afferente signalen alleen kunnen geen informatie verschaffen over onze armlengte of -breedte, er moet worden verwezen naar opgeslagen lichaamsrepresentatie die de metrische eigenschappen van ons lichaam 'kent'. Volgens Longo en Haggard (2010) behoudt dit lichaamsmodel vervormingen van de somatosensorische cortex op een verzwakte manier. Deze vervormingen zijn niet zichtbaar in het bewuste lichaamsbeeld (een visueel beeld van ons lichaam), en Longo behandelt deze twee representaties als verschillend (Longo en Haggard (2012) en aan tegenovergestelde uiteinden op hetzelfde continuüm (Longo & Haggard, 2017). Aan de ene kant van het continuüm is er sprake van een expliciete visueel gebaseerde lichaamsrepresentatie en aan de andere kant een representatie op basis van somatosensatie die sterk vervormd is. Kortom, onder bepaalde omstandigheden nemen we ons lichaam waar als sterk vervormd, dat wil zeggen dat verschillende representaties langs een continuüm worden gekenmerkt door verschillende wegingen van somatosensorische representaties en een visuele representatie, en daarom kunnen vervormingen in grootte verschillen. Er zijn dus aanwijzingen dat verstoringen in de manier waarop we ons lichaam waarnemen lijken voort te komen uit zowel centrale als perifere processen.

Vraagstellingen

In mijn proefschrift was mijn doel te onderzoeken hoe en in welke mate primaire sensorische input hogere orde representaties kan beïnvloeden. Als primaire sensorische input deze representaties moduleert, wat zijn dan de implicaties voor patiëntengroepen waar primaire sensorische input wordt aangetast door hersenbeschadiging? Mijn proefschrift behandelt dit in twee delen. In het eerste deel concentreer ik me op lichaams- en ruimte gerelateerde interacties bij gezonde individuen, in het tweede deel richt ik me op dezelfde interacties bij patiënten.

In het eerste deel, bij gezonde controles, wil ik eerst begrijpen of hand *ownership* anders wordt ervaren voor de linker- en rechterhand, en of handigheid een differentiële impact heeft op die ervaring. Met andere woorden, is *hand ownership* gelateraliseerd? Vervolgens ga ik een stap verder en ga ik na of we daadwerkelijke tactiele input nodig hebben om *hand ownership* te ervaren. In eerdere paragrafen heb ik de handvervormingen uitgebreid besproken, en mijn vraag is of we de waargenomen vorm van de hand kunnen veranderen door sensorische input te moduleren. Mijn volgende vraag is of veranderingen in de lichaamsrepresentatie tijdelijk kunnen veranderen hoe we de ruimte rond dat lichaamsdeel waarnemen. Antwoorden op deze deelvragen zullen ons inzicht geven of veranderingen van primaire (multi)sensorische input hogere orde lichaams- en ruimterepresentaties bij gezonde individuen kunnen beïnvloeden. In het tweede deel wil ik de resultaten die gevonden zijn in gezonde controles op de proef stellen, dat wil zeggen, ik zou graag inzicht willen krijgen in wat er gebeurt als feitelijke sensorische informatie wordt aangetast, bijvoorbeeld na een beroerte. Heeft verminderde afferente input invloed op hogere orde representaties? Concreet stel ik de vraag of intacte somatosensatie noodzakelijk is om informatie over lichaamsafmetingen te verkrijgen. En, moduleert de afwezigheid van deze signalen *hand ownership*? In dit deel zal ik ook een casus presenteren die lichamelijke problemen van hogere orde rapporteert, d.w.z. een volledig gebrek aan *body ownership*, ondanks intacte afferente signalen (signalen naar het lichaam toe). Hier vraag ik me af of ik de multisensorische signalen kan moduleren om problemen van de patiënt te verlichten. In het laatste deel vraag ik me af of herhaalde toepassing van transcraniële gelijkstroomstimulatie op de pariëtale cortex de symptomen van ruimtelijk neglect zal verlichten. Antwoorden op deze vragen zullen inzicht geven in of multisensorische input noodzakelijk is om informatie over lichaamsafmetingen te verkrijgen, en of het *hand ownership* beïnvloedt.

Antwoorden

De hoofdstukken 2 t/m 5 hebben begrip van de lichaamsrepresentatie bij gezonde individuen vergroot, meer specifiek bieden deze hoofdstukken inzicht of modulaties van primaire (multi)sensorische input hogere-orde lichaams- en ruimterepresentaties bij gezonde individuen beïnvloeden. Ten eerste ontdekte ik dat er geen handlateralisatie-effect was voor visuotactiele integratie en *body ownership*, en het maakte ook niet uit of de illusie werd toegepast op de linker- of de rechterhand. Gezien de bevindingen vind ik het waarschijnlijk dat gevoelens van *ownership* misschien niet zo gelateraliseerd zijn als de huidige literatuur aangeeft en dat handrepresentaties in de hersenen gelijk kunnen zijn voor de linker- en rechterhand tijdens de rubber hand illusie. Vervolgens ontdekte ik dat we niet per se een echte aanraking nodig hebben om eigenaar te worden van een nephand. Ik stel daarom voor dat ons brein bottom-up multisensorische informatie gebruikt, evenals top-down voorspellingen over verwachte sensorische input om onze hand weer te geven. Daarnaast werd gevonden dat synchrone multisensorische stimulatie in tegenstelling tot asynchrone stimulatie de waargenomen actieruimte naar de nephand kan verschuiven. Belangrijk hierbij is dat de subjectieve ervaring van de illusie niet samenhangt met deze verschuiving in de ruimte, terwijl de proprioceptieve drift/positiezin dat wel doet. Het lijkt dus waarschijnlijk dat multisensorische integratie van lichamelijke informatie deze verschuiving in PPS aanstuurt en niet gevoelens van hand eigenaarschap op zich. Ten slotte laat ik zien dat we onze handen als sterk vervormd ervaren; een overschatting van de breedte en een onderschatting van de lengte. De algemene vorm van de hand werd breder waargenomen dan lang. Wat verrassend was, was dat deze waarneming robuust was voor de meeste sensorische modulaties (d.w.z. proprioceptief, tactiel en geen input). Toen de vinger echter bewoog, werden de waargenomen vervormingen iets sterker. Ik concludeer daarom dat de impliciete representatie van onze hand afhankelijk is van een opgeslagen lichaamsmodel, dat niet wordt beïnvloed door de modulatie van sensorische input.

De hoofdstukken 6 t/m 8 vergroten ons begrip van de representatie van het lichaam en de ruimte bij patiënten met verworven hersenschade. Ten eerste vonden we dat patiënten met somatosensorische stoornissen hun hand als (even) vervormd ervaren als gezonde individuen; brede korte handen. Een paar patiënten zagen hun aangedane hand als onevenredig groot, wat mogelijk verband houdt met een verminderd lichaamsbewustzijn en sensomotorische stoornissen. Zoals verwacht hadden de meeste patiënten een waarheidsgetrouw beeld van hun bewuste hand, zoals beoordeeld met de taak voor het matchen van handsjablonen. Opvallend was dat patiënten in de ernstig aangedane groep de algehele vorm als minder waarheidsgetrouw ervoeren dan patiënten met matige tactiele problemen en gezonde controles. In feite, in tegenstelling tot de somatosensorische representatie, zagen ze de algehele vorm van de hand als langer dan breed. Ik suggereer dat dit het resultaat is van een visueel-tactiele herschaling; een visuele correctie van de vervormde corticale somatosensorische representatie, maar dat deze correctie overbodig wordt wanneer somatosensorische informatie ontbreekt, aangezien er dan niets te herschalen is. Vervolgens ontdekten we dat een patiënt zonder primaire somatosensorische (en visuele) stoornissen nog steeds zijn lichaam als niet van hem kan beschouwen. Bij deze patiënt leek er sprake van een te grote afhankelijkheid van visuele input in plaats van het combineren van visuele en somatosensorische input, hetgeen wijst op suboptimale multisensorische integratie. Bovendien ontdekten we dat oefeningen die visuele input over het lichaam vanuit een derde persoonsperspectief (d.w.z. door een spiegel) in combinatie met tactiele stimulatie (wrijven over een arm) omvatten, zijn lichaamsbewustzijn verbeterden. Ten slotte verbeterde het herhaaldelijk met tDCS behandelen van patiënten met visuospatieel neglect hun gelateraliseerde problemen niet. Gezondheids- en veiligheidskwesties waren beperkende factoren in deze studie.

Theoretische implicaties en toekomstige richtingen

Wat kunnen de bovengenoemde bevindingen ons vertellen over modellen van lichaamsrepresentatie en ruimterepresentatie bij gezonde individuen en klinische groepen?

We kunnen uit de eerdere studies concluderen dat er een complexe interactie is tussen somatosensorische input, multisensorische integratie, ervaren lichaamseigendom en de representatie van de ruimte om ons heen. De relatie tussen deze processen is soms duidelijk, maar soms ook niet. De uitdaging is hoe de precieze relatie tussen beide te definiëren: metrische relaties lijken bijvoorbeeld niet afhankelijk te zijn van directe sensorische signalen, maar zijn eerder afhankelijk van een opgeslagen representatie van onze ledematen. Een gevoel van *ownership* over onze ledematen is niet noodzakelijkerwijs afhankelijk van somatosensorische input, en lijkt afhankelijk te zijn van multisensorische integratie en/of visuotactile voorspelling. Dit kan gevolgen hebben voor bepaalde patiëntengroepen die minder *ownership* voelen, bijvoorbeeld door suboptimale multisensorische integratie. Als lichaamseigendom kan worden gemoduleerd door top-down voorspellingen, dan kunnen deze groepen profiteren van dit top-down mechanisme bij het behandelen van *ownership*. Bovendien zou de modulatie van het *type* aanraking ook veelbelovend kunnen zijn, aangezien verschillende soorten aanraking de rubber handillusie kunnen moduleren en hand *ownership* kunnen beïnvloeden. Er zijn aanwijzingen dat affectieve, tactiele input de subjectieve ervaring van de illusie kan veranderen in positiezin (van Stralen et al., 2014) en subjectieve ervaring van *ownership* (Crucianelli, Metcalf, Fotopoulou, & Jenkinson, 2013). Affectieve aanraking kan worden omschreven als langzame aanraking (1-10 cm/s), en typisch zullen de niet gemyeliniseerde C-vezels, naast Aβ-vezels, reageren. Discriminerende of niet-affectieve aanraking wordt meestal beoordeeld door veel sneller (30 cm/s) te strelen, waardoor alleen de Aβ-vezels worden geactiveerd. Een netwerk van hersengebieden is verschillend betrokken bij elk type aanraking. Over het algemeen is discriminerende aanraking gekoppeld aan de primaire somatosensorische cortex en affectieve aanraking is gekoppeld aan het achterste deel van de insula. Interessant is dat het achterste deel van de insula is gekoppeld aan lichaamsbewustzijn (Baier en Karnath, 2008, Tsakiris et al., 2007, Tsakiris, 2010, Tsakiris et al., 2011). Dit is van bijzonder belang wanneer de normale aanraking afwezig is of verminderd is als gevolg van schade aan de pariëtale gebieden. Voor lichaamseigendom kan multisensorische integratie verzwakt zijn doordat de discriminerende tast 'kanalen' in deze groep meestal aangedaan zijn en ze minder tactiele en proprioceptieve input krijgen. Het gevolg is dat er meer gewicht wordt gegeven aan visuele input. Het visueel vastleggen van de rubberen hand in combinatie met een zwakker tastwaarneming en proprioceptie, resulteert in een grotere illusie van een rubberen hand, zoals is aangetoond in eerdere studies (Burin et al., 2015; Smit et al., 2019). Affectieve aanraking kan, door de alternatieve route te stimuleren, een deel van de tastzin herstellen, die voorheen verloren of verminderd was (Jenkinson, Papadaki, Besharati, Moro, Gobbetto et al., 2020). Dit idee hebben we in hoofdstuk 7 gepresenteerd (Smit, Van Stralen, Van den Munckhof, Snijders & Dijkerman, 2019). Hoewel deze patiënt geen somatosensorische problemen had, ervoer hij wel een verminderd eigendom over zijn hele lichaam na een parietotemporale tumorresectie, die lijkt voort te komen uit suboptimale multisensorische integratie, d.w.z. een te grote afhankelijkheid van visuele input. Affectieve aanraking verhoogde het gevoel van eigenaarschap, wat tot uiting kwam in een vergelijkbaar patroon van resultaten als gezonde controles in de rubberen handillusie. Kortom, de differentiële rol van aanraking en bottom-up sensorische integratie behoeft nadere aandacht, gezien veelbelovende voorlopige resultaten zou toekomstig onderzoek zich kunnen richten op modulatie van aanraking door ofwel bottom-up affectieve aanraking, en/of top-down voorspellende mechanismen.

Conclusie

Al met al dragen de resultaten van dit proefschrift bij aan ons begrip van lichaamsperceptie, multisensorische representaties, ruimteperceptie en de complexe interactie daartussen. Met mijn studies wilde ik ons begrip van hand- en ruimterepresentaties bij gezonde individuen en bij individuen met niet aangeboren hersenschade vergroten. De resultaten van deze studies leren ons dat niet alleen visuotactile integratie, maar ook visuotactile voorspelling een gevoel van eigenaarschap over een vreemd object kan veroorzaken en dat het bieden van een combinatie van 3e persoonsperspectief en aanraking het gevoel van *body disownership* bij een patiënt kan verminderen. Ook kan multisensorische integratie van lichamelijke informatie de waargenomen peripersoonlijke ruimte veranderen. We ontdekten verder dat hoe de hand wordt waargenomen, over het algemeen vergelijkbaar is voor gezonde personen en voor personen met somatosensorische tekorten na verworven hersenbeschadiging. Over het algemeen geven deze bevindingen meer inzicht in de complexe wisselwerking tussen somatosensorische verwerking, waargenomen lichaamsgrootte en *ownership* en ruimteperceptie en zijn als zodanig consistent met modellen zoals de lichaamsmatrix (Moseley et al., 2012; Riva, 2018). De uitdaging voor toekomstige studies is om te bepalen hoe de verschillende componenten op elkaar inwerken en wat de onderliggende mechanismen zijn.

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CURRICULUM VITAE

Miranda Smit was born in Dedemsvaart, the Netherlands on February 13th 1983. She graduated from secondary school at Vechtdal College. She studied Psychology in Utrecht. During her bachelor she became interested in neuropsychology and neuroscience. After obtaining her bachelor’s degree, she graduated the academic master Neuropsychology cum laude. After graduation she continued to combine clinical work as a neuropsychologist and research during her PhD (under supervision of Chris Dijkerman, Maarten van der Smagt and Ineke van der Ham). She is currently working as a (medical) psychologist in training for healthcare psychologist (under supervision of Astrid Blok, Wisse van den Berg, Marieke Boon en Metha Klaver) at Noord-West Hospital in Alkmaar.

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