Stroke & Body Ownership

Haike Eva van Stralen

Cover Design by: Studio Bullseye, Amersfoort, The Netherlands
Layout: Legatron Electronic Publishing, Rotterdam, The Netherlands
Printed and layout: Ipskamp printing, Enschede, The Netherlands

ISBN is 978-90-393-6980-7

PhD thesis, Utrecht University, The Netherlands
Haike Eva van Stralen, 2018

Stroke & Body Ownership

Lichaamsbewustzijn, aanraking en beroerte

(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 8 juni 2018 des middags te 12.45 uur.

door

Haike Eva van Stralen

geboren op 22 april 1983 te Leusden

Promotoren: Prof.dr. H.C. Dijkerman
Prof.dr. L.J. Kappelle

Copromotor: Dr. M.J.E. van Zandvoort

Dit proefschrift werd (mede) mogelijk gemaakt met financiële steun van NWO Vici-beurs 453-10-003 to HCD.

Table of Contents

Chapter 1

General introduction

H.E. van Stralen

> “Easy!” I said. “Be calm!” Take it easy! I wouldn’t punch that leg like that.
> “And why not!” he asked, irritably, belligerently.
> “Because it’s your leg”, I answered. “Don’t you know your own leg?”
> *Sacks,* The man who Mistook his Wife for a Hat.

Feeling touch is of crucial importance in daily life. It enables us to experience the warmth of a cup of coffee in the morning, grasp our keys from our purse and enjoy the pleasant feeling of a loving caress. When the sense of touch gets disturbed, we experience the world around us differently. Not getting alarmed by a cup of coffee that is too hot may lead to hazardous situations, and grabbing your wallet instead of your keys results at least in some frustration. An interesting aspect of the sense of touch is that it not only gives information about the world around us; keys or coffee, but is also generates information about ourselves. Lifting the cup of coffee from the table gives us an idea about the length of our arm. Taking a sip from a cup of coffee requires a representation of the configuration and position of our arm. Conversely, this interaction generates feedback information that updates the body representation. That is, touching the cup with your lips reveals that your hand is closely located to your mouth. And this information contributes to the idea that the hand that is holding the cup, is in fact *your* hand. This sense of body ownership is a feeling that seems self-evident. You know what your arm looks like and how it feels, and you just *know* that it belongs to you. This belief is stable over lifetime, and gets hardly disturbed. For example, your hand covered with soap while showering does not change our belief that these odd looking hands are yours. The same holds for hands that feel extremely cold during winter, they remain your hands. The feeling of ownership is therefore a firm belief, and when it gets disturbed our ideas about ourselves and the world are revealed. Unfortunately there are cases in which the sense of ownership gets distorted, in some cases even permanently. In these cases, there is confusion whether they own certain body parts, usually the leg or arm. Or in some cases there is a complete rejection of the idea of having a limb. One can only imagine how debilitating this must be. Or as one of the patients put it: ‘If I am not certain that my arm is mine, then what certainty do I have, that I am myself?”.

A large body of research has focused on the basic mechanisms of touch, such as the perception of touch, temperature and pain. However, the cases with body ownership impairments exemplify that disorders in the sense of touch can have numerous consequences beyond problems in the sensitivity for pressure or texture. In this thesis, we will focus on these higher order aspects. And that is; how do we perceive our body? To be more specific; what goes on when there are misperceptions of the body?

This thesis consists of nine chapters. In **Chapter 2** we provide an overview of the wide variety of impairments of the somatosensory function that is caused by a lesion of the central nervous system. These impairments can occur on multiple levels ranging from primary touch perception disorders, such as the inability to detect texture on a piece of sandpaper to higher order disorders such as recognizing the keys in your pocket, or knowing that your hand is yours.

In **Chapters 3** and **4,** we demonstrate two case studies that show a rare and unique impairment in body ownership after an acquired brain lesion. Clinicians often fail to detect body ownership impairments. In the case that these disorders are present, systematic investigation of these patients is challenged by the presence of other (sensory, motor and cognitive) disorders, since body ownership impairments are often the result of large brain lesions. As a consequence, standard experimental set-ups that have been developed to examine specific body ownership problems, may not be suitable for patients that can not sit up straight because of motor impairments. Also, patients with cognitive impairment may fail to understand task instruction or cannot respond to questionnaires. Therefore, the underlying mechanisms of these phenomena in patients with large brain lesions remain largely unknown. The two patients we report in **Chapters 3** and **4** suffer from a diminished feeling that their limbs belong to themselves. These cases are unique for two reasons. First, neither recovered from their body ownership impairments, resulting in a chronic state of body ownership impairments. Second, both patients proved to have intact primary somatosensory functioning such as pressure sensitivity and position sense. These two features made both patients suitable for an experimental investigation that contributed to a better understanding of body ownership impairments.

Meeting and examining patients sometimes leads to so much information, that this cannot be summarized in a scientific paper. It leads to new hypotheses and shapes our insights on the underlying mechanisms and potential rehabilitation methods. An example of this cycle is a patient who after a large haemorrhagic stroke, had signs of rejection and feelings of hatred towards her paralyzed arm (**Chapter 5**). I visited her on a daily basis and witnessed her recovery in which the body ownership impairments seem to fade. During this process, the patient stroked, touched and caressed her affected arm frequently. She even kissed her affected arm sometimes. When asking her why she felt the urge to do so, she replied that 'being loving to the arm would make it feel as my arm again'. Her report and behaviour made me think whether this would have indeed contributed to the re-instalment of her feeling of ownership over the affected arm. We therefore experimentally investigated whether touching her own hand and other fake hands altered her feeling of ownership. Furthermore, we conducted a review of the literature on the effects of self-touch and the somatosensory function, with an emphasis on the higher order aspects of the somatosensory functioning. Moreover, we experimentally investigated the effects of affective, pleasant touch on body ownership in healthy participants in **Chapter 6.** Studies in healthy participants offer great advantages, since a larger number of test conditions is possible, and the experimental time and number of participants are less restricted compared to patient studies. Important for affective, pleasant touch is stimulation of a set of receptors that respond to soft, slow stroking at about 3cm/s. This slow stroking is associated with pleasant touch and is processed differently, via the so-called unmyelinated c-tactile fibres, from discriminative touch (McGlone, Vallbo, Olausson, Loken, & Wessberg, 2007; Olausson et al., 2002). In **Chapter 6,** the influence of pleasant touch on body ownership was investigated. This was investigated by a well-known and often used illusion that can be elicited in healthy participants to influence the sense of body ownership. This illusion is called 'The Rubber Hand Illusion' (RHI) (Matthew Botvinick & Cohen, 1998). In this illusion, a visible rubber hand is stroked in synchrony with an invisible real hand that induces a feeling of ownership over the rubber hand. Participants feel as if the rubber hand is their own hand, and sometimes feel as if their own real hand gets disowned. The strength of the illusion is reflected in a subjective report (questionnaire) and an objective measure 'proprioceptive drift'. Proprioceptive drift represents a perceptual change in estimated hand position. In case of a strong illusion, participants feel as if the position of their stimulated hand has been shifted towards the rubber hand. More recent studies proposed another outcome measure as an indication of the strength of the Rubber Hand Illusion, and that is the temperature of the hand (Moseley et al., 2008).

In **Chapter 6**, the strength of the RHI was measured between different stroking conditions, i.e. slow stroking versus regular stroking. In addition, slow stroking on skin that contains c-tactiles fibers was compared to slow stroking on skins that does not contain c-tactile fibers. The strength of the RHI was measured by prorioceptive drift, subjective reports and temperature changes of the hand. It has been suggested that a drop in temperature of the hand reflects a mechanism of disownership of the real hand. However, in the studies in the current thesis as well as other studies, this has not been found consistently. We therefore conducted a a meta-analysis on temperature changes of tha hand to investigate whether a drop in hand temperature is a reliably proxy of the RHI.

Somatosensory information originating from the external world or from within our body almost never occur in isolation, that is, in the absence of visual, auditory, and/or olfactory stimulation. Thus, the meaning, the perception and the value we attribute to the somatosensory information depend also on other sensory and cognitive modalities. It involves other cognitive functions such as spatial cognition, attention, and executive functioning. The relation between the somatosensory abilities and other cognitive functions, however, is not clear. Therefore we conducted a study in patients who suffered a stroke, and assessed them with a neuropsychological test battery including tests targeting the somatosensory system. In this study, we focused on the ability to distinguish left from right, i.e. left right orientation, since previous research has suggested that this ability is associated with the sensorimotor function (Parsons, 1987; Sekiyama, 1982). In order to link disorders in left right orientation and the somatosensory system to neurological correlates, we conducted a Voxel-based Lesion Symptom Mapping (VLSM) analysis. With this neuroimaging analysis technique, the relationships between behavioral deficits in neurological populations and lesion sites associated with those deficits are investigated. I report this study and results in **Chapter 8.** I conclude this thesis with a general discussion in **Chapter 9.**

Chapter 2

Central touch disorders

H.E. van Stralen
and
H.C. Dijkerman

As published in: Scholarpedia, 6(10):8243, 2011.

H.C.D. designed research; H.E.S., and H.C.D. performed research and wrote the paper.

Introduction

Central touch disorders comprise a wide range of deficits in somatosensory perception than can occur after damage to the central nervous system. They vary from deficits in the detection of a touch to complex cognitive deficits such as the inability to recognize objects through touch or the experience of having an additional body part such as a third arm. To understand these disorders, first the neural pathways involved in tactile information processing in the central nervous system will be summarized. This is followed by an overview of the touch disorders ranging from primary-, to higher order deficits.

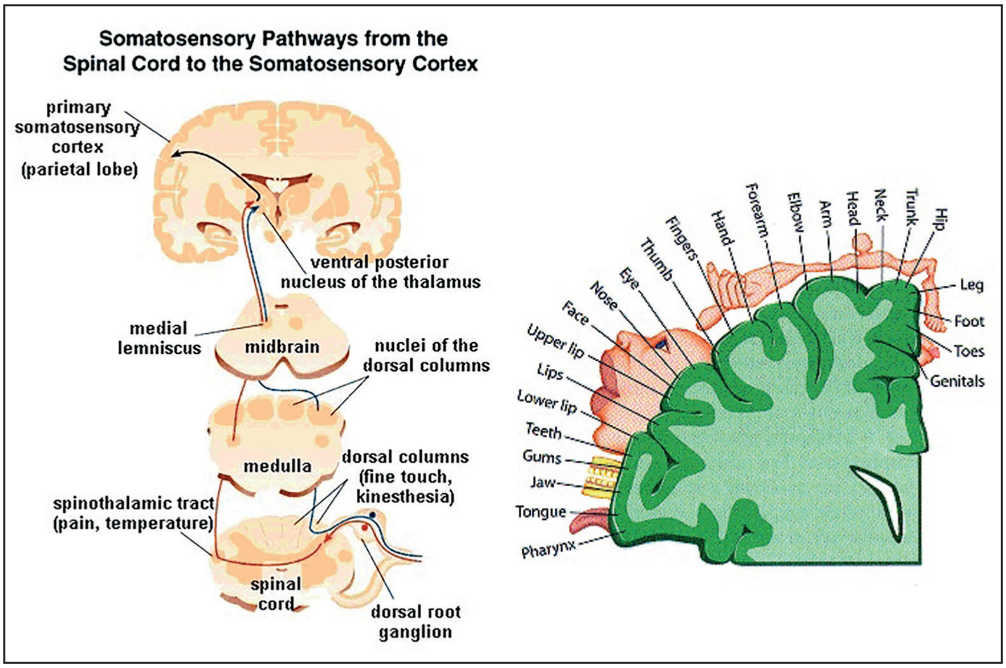

Figure 1 | a): The somatosensory ascending pathways responsible for conveying somatosensory input to the brain. b): The SI of each hemisphere contains somatotopic maps of the contralateral side of the body.

Pathways of tactile information processing in the Central Nervous System

Tactile information is processed within the somatosensory system. Somatosensory input is derived from a variety of receptors in the skin, muscles and joints which convey information about different elementary sensory modalities such as i) discriminative touch (pressure, vibration), ii) proprioception which concerns information about the position and movement of one's own body and limbs, iii) pain and sensitivity to hot and cold and iv) affective touch (induced by slow stroking with a soft brush) (McGlone et al., 2007; India Morrison, Löken, & Olausson, 2010) each relaying tactile, thermal, painful, or pruritic (itch). Two ascending systems are responsible for conveying somatosensory input to the brain. The medial lemniscal system is involved in discriminative touch and proprioception, while the spinothalamic tract mediates pain, thermal and affective tactile information. The medial lemniscal two system projects contralaterally to the thalamus after which most somatosensory input is relayed to the primary somatosensory cortex (SI), located in the anterior parietal cortex (see Figure 1a).

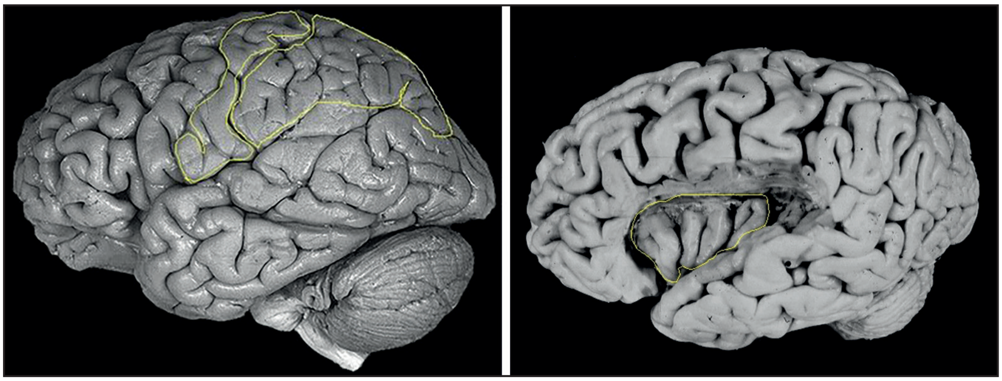

Figure 2 | a): The spinothalamic system projects to the outer layers of the spinal dorsal horn from whether projections exist via a thalamic relay nucleus (VMpo) to the posterior insular cortex. The somatosensory system located in the anterior parietal cortex. b): The insula is located beneath the frontal, parietal and temporal opercula and is involved in affective touch, pain and temperature sensitivity and in higher order tactile processing. *From: the digital anatomist project in the department of biological structure at the University of Washington*

The SI of each hemisphere contains somatotopic maps of the contralateral side of the body. In these somatotopic maps, each body part is represented according to the degree of innervation density, e.g. body parts with higher receptor density occupy larger areas in SI (Penfield, 1950), see Figure 1b. Damage to SI is associated with primary discriminative tactile processing disorders, i.e. impairments in processing the physical, elementary characteristics of tactile stimuli. The posterior insular cortex also contains somatotopic maps for pain, temperature sensitivity and affective touch (Björnsdotter, Löken, Olausson, Vallbo, & Wessberg, 2009). Higher order somatosensory processes involve wider more distributed networks, including the secondary somatosensory cortex (SII), the posterior parietal cortex and the anterior insula, see Figure 2.

The higher order processes range from extracting the features of an object, to the recognition of an object and to body-perception related processes. In contrast to the contralateral involvement for primary tactile information, higher order processes can be bilaterally disturbed after a unilateral lesion. For example, a right hemispheric lesion can cause problems in object recognition in the left hand as well as in the right hand. In addition, there is growing evidence for hemispheric specialization in higher order tactile processes, where right-sided brain lesions result in more severe spatial defects (Heilman, Bowers, Valenstein, & Watson, 1986; Heilman, K.M., & Valenstein, 2010) or impairments in body awareness (Karnath & Baier, 2010) compared to left-sided lesions. No hemispheric lateralization for primary (elementary) tactile function appears to exist.

Overview of Central Touch Disorders

Primary somatosensory disorders

Primary tactile disorders consist of an inability to detect elementary somatosensory aspects, including impaired sensitivity to pressure applied to the skin, elevated two-point discrimination thresholds (i.e. impaired spatial acuity), loss of vibratory sense, or deficits in proprioception. Primary tactile impairments have been reported usually after damage to the contralateral SI, the thalamus, or the subcortical ascending somatosensory pathways. These deficits can selectively affect one somatosensory submodality while others remain functionally intact (Corkin, 1978). For example, some patients are able to feel hot and cold while they have no sense of where their limbs are when they have their eyes closed. This is consistent with the idea that these features are processed in parallel. Obviously, primary tactile disorders can lead to problems in higher order touch disorders such as an inability to recognize objects by touch. However, higher order tactile disorders can be present in the absence of primary elementary defects (Bohlhalter, Fretz, & Weder, 2002).

Higher order touch disorders

Discrimination of features

A next hierarchical level in the somatosensory processing of stimuli, is the discrimination of haptic features. The term haptic is used here to show that it involves more than just passive tactile input, but a combination of tactile and proprioceptive information gained through active exploratory hand movements (see below under Object exploration). Haptic features include texture, substance, size, shape, weight and the hardness of a stimulus. Evidence from studies with healthy participants suggests that haptic object feature discrimination can be designated into two categories, i.e. pertaining to the micro- and macrogeometrical properties of an object (Morley et al. 1983). Texture, density or thermal properties are regarded as the microgeometrical aspects, whereas size and shape are regarded as macrogeometrical properties. Evidence for this segregation stems also from reports of selective dissociated impairments within tactile feature discrimination (Delay, 1935). That is, hylognosia is an impairment that is characterized by the inability to discriminate texture, density or the thermal properties of an object (microgeometrical). Conversely, suffering from morphognosia means that the patient has an inability to discriminate the size of shape of an object (macrogeometrical). Is has been found that discriminating microgeometrical properties of an object is associated with activation in the parietal operculum (Roland, 1987) whereas the anterior part of the intraparietal sulcus is predominantly associated with processing macrogeometrical properties, suggesting that these two functions are segregated on a neuroanatomical level as well (Caselli, 1991; Hömke et al., 2009; Reed, Caselli, & Farah, 1996). However, other reports have disputed the theory of two separate feature processing disorders. It has been argued that impairments in perceiving macrogeomatrical properties of an object is a consequence of impaired spatial abilities. For example, perceiving the size or shape of an object requires for an analysis of the direction and extension of the movement, the sense of limb position in space and tactile localisation (Saetti, De Renzi, & Comper, 1999). However, some reported patients with morhphognosia showed no spatial deficits in other (visual) modalities (Reed et al., 1996) or only mild spatial deficits (Delay, 1935)

Object exploration

Discrimination of features and recognizing an object through touch is not a passive process and requires hand movements to interact with the object. These are stereotypical hand movements that are elicited spontaneously through interaction with an object by touch (Lederman & Klatzky, 1987). The type of hand movements depends on the object characteristics we want to extract. Deficits in making these hand movements at this level are called tactile apraxia, in which difficulties arise in attuning hand movements to the characteristics of an object in the presence of preserved elementary motor or sensory abilities, see Figure 3. Tactile apraxia is usually associated with damage to superior posterior parietal areas (Binkofski et al., 1999; Seitz et al., 1999). Not surprisingly, difficulties in the exploration of an object can lead to problems in object recognition (Valenza et al., 2001), although this is not obligatory (Caselli, 1991). In the case of problems in object recognition, different causes can underlie this deficit. In the next paragraph, the haptic recognition of objects and their associated disorders are discussed.

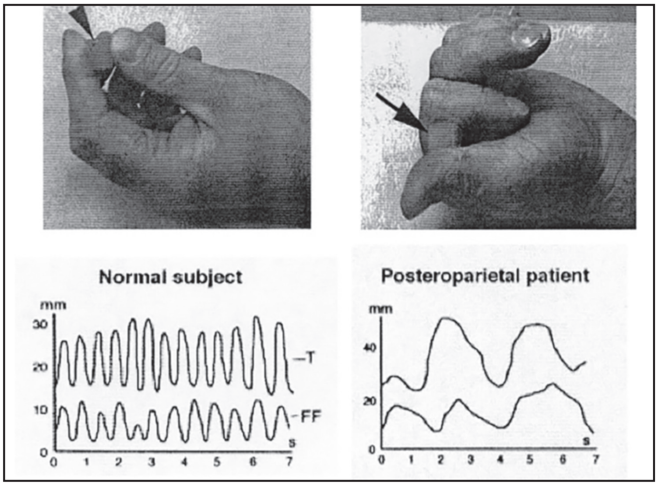

Figure 3 | Difficulty in attuning hand movements to the characteristics of object in a case of tactile apraxia. *From: Binkofski et al. 2001*

Object recognition

Besides intact somatosensory processing at lower levels and purposeful exploratory hand movements, multiple somatosensory signals have to be combined to form a representation of an object. An example is when you try to grasp your keys from your pocket. This requires purposeful hand movements to search for the expected object features, for example a flat, hard, cool object with a circular shape on one end and ridges on that other end. The information then needs to be integrated into a coherent representation of an object. Subsequently, the semantic properties (its use and function) are retrieved. A deficit in building the object representation or in accessing the semantic properties of the object is called 'tactile agnosia' (Caselli, 1991; Delay, 1935; Endo, Miyasaka, Makishita, Yanagisawa, & Sugishita, 1992; Reed & Caselli, 1994; Reed et al., 1996). In tactile agnosia, primary somatosensory processing as well as object recognition through other modalities are usually preserved. The level at which an abnormality in information processing occurs in tactile agnosia can vary. First, the integration of the micro- and/or macrogeometrical properties into a coherent representation of the object can be impaired, which is called tactile apperceptive agnosia or astereognosis. These patients are unable to draw the object they have explored through touch. Clinical reports of apperceptive agnosia without primary somatosensory or motor deficits are rare and are often linked to right hemispheric damage. Since the right hemisphere is associated with spatial perception, some authors have suggested that higher order tactile disorders are merely a consequence of impairments in spatial skills ((Semmes & Mishkin, 1965; Sterzi et al., 1993). Indeed, somatosensory impairments often occur together with deficits in higher order spatial processing such as neglect. More recent studies, however, reported that tactile agnosia can exist without spatial deficits (Reed et al., 1996; Saetti et al., 1999). The second type of haptic object recognition deficit is tactile associative agnosia and occurs when a representation of object is achieved (i.e.. the patient can make a drawing of the object), but when access to semantic knowledge of the object is is lost, therefore preventing recognition. Recently, a case of pure associative agnosia of the left hand has been described (Veronelli, Ginex, Dinacci, Cappa, & Corbo, 2014). A right haemorrhagic lesion limited to the post-central and supra-marginal gyri resulted in an inability to recognize objects in only the left hand, with a preserved tactile discrimination or visuo-tactile matching of objects. Thus, patients with associative tactile agnosia can describe the object (e.g. a metal object with an irregular side in case of a key) but are not able to indicate either the use nor name the object. To access this semantic knowledge, input from memory storage about this object is needed (Mesulam, 1998). Furthermore, prior semantic knowledge about an object improves tactile recognition performance, suggesting that top-down mechanisms are involved in tactile processing (Bohlhalter et al., 2002).

Another haptic object recognition disorder is tactile aphasia (anomia), where the patient is unable to name the object when perceived by touch. Interestingly, the patient is capable of naming the object when it is perceived through another modality. In addition, patients can pantomime the use of a tactile presented object or are able to categorize objects by their meaning, indicating that the semantic knowledge of the object is accessible. Whether the semantic knowledge of the object is completely intact remains controversial but it is clear that semantic problems do not fully account for the problems in naming the object. Thus, a patient with tactile aphasia would be able to successfully discriminate his key from the coins in his pocket. He is capable to describe that this is the object for opening his front door, although he is unable to come up with the word 'key'. When he can see the key (other modality), he immediately is able to name it. Although not many case studies on tactile aphasia have been described, there is evidence that tactile aphasia and tactile agnosia are different on symptomatology as well as the neuroanatomical substrate (Endo et al., 1992).

The somatosensory system is not only important for recognizing external stimuli such as objects, but primarily provides information and a conscious experience about the body of the observer. A wide range of disorders in bodily experience after damage to the central nervous system has been reported. In the next section an overview of these deficits is given.

Body related disorders

Information about our body is based on an integration of visual, vestibular, proprioceptive and tactile input. Several authors have proposed that different representations of our body exist and a common distinction is that between body image and body schema (Gallagher, 2005; Paillard, 1999), (see de Vignemont 2010 for a critical appraisal of this idea). The body image represents a conscious 'perceptual identification of body features'. It may be more visually based and is influenced by stored knowledge about the body structure and semantics as well as by bottom-up incoming sensory input. In contrast, the body schema codes the position of body parts in space for the guidance of action and is mainly based on tactile input combined with proprioceptive information. The body schema is continuously updated as our body moves or changes. The cerebral basis of the body schema is still unclear, though a central role for the superior part of the posterior parietal cortex has frequently been suggested (Dijkerman & de Haan, 2007). Disorders in the body representations may include features of both types. An alternative organization with respect to the role of the somatosensory system to body representations is proposed by Longo and colleagues (Longo, Azañón, & Haggard, 2010). They described different levels of processing with somatosensation being the lowest (linked to a primary somatosensory processing in SI). Somatoperception concerns the process leading to bodily perception especially related to achieving perceptual constancy. Finally, somatorepresentation refers to more cognitive processes that result in building semantic, configural and emotional knowledge and attitudes about the body. Both somatoperception and somatorepresentation seem to be linked more to the concept of body image rather than the action related body schema. In the next two paragraphs, we will describe a few examples from the huge variety of disorders that exists and we will link them to some of the more cognitive concepts described above.

Structural body representation disorders

Structural body representation concerns the knowledge about the arrangement and form of body parts, crucial to form a sense of body awareness. In "autotopagnosia", patients are unable to point to their own body parts on a visual scheme (Poeck & Orgass, 1971; Semenza & Goodglass, 1985), whereas in heterotopagnosia problems arise in pointing to somebody else's body parts. These disorders have been associated with middle-temporal or parietal lesions of the dominant hemisphere (John Schwoebel & Coslett, 2005). Structural body representation disorders not necessarily affect the whole body, but can be selectively impaired for the fingers, in the case of "finger agnosia" in which patients are unable to identify the fingers despite a preserved ability to use them (Gerstmann, 1940a; Kinsbourne & Warrington, 1963). It usually affects the middle three fingers of both hands (Frederiks, 1985). Although finger agnosia was initially regarded as a form of autotopagnosia (Gerstmann, 1940a), the disorders appeared to be dissociated (De Renzi & Scotti, 1970). Finger gnosis has been repeatedly associated with bilateral parietal activation (Rusconi, Walsh, & Butterworth, 2005). The bilateral parietal lobe has been repeatedly associated with finger gnosis. A recent study on the neuroanatomical correlates of finger gnosis specified that left anteromedial parietal lobule plays an important role in finger identification (Rusconi et al., 2014). Finger agnosia can be considered to be a body image deficit, as tactile input to individual fingers can be used correctly to guide movements (Anema et al., 2008). Traditionally, finger agnosia was not regarded a unitary phenomenon, but has been described a part of a cluster of impairments, known as the Gerstmann syndrome (Gerstmann, 1940a). Gerstmann syndrome is characterized by four core symptoms, i.e. finger agnosia, dyscalculia, dysgraphia and left-right orientation. The latter is also regarded as a body representation disorder and concerns the impairment in the identification of the left and right side of one's own, but also someone else's body. In addition to deficits in structural and spatial aspects of body representation, disturbances in body size perception have also been reported. Macrosomatognosia refers to the perception of a body part being larger than it's actual size, while in microsomatognosia patients experience their body (part) as being smaller (Frederiks, 1985). These deficits have been associated with a range of paroxysmal disorders such migraine or seizures and often occur temporarily (Rode et al., 2012). They also have been reported for the affected hand in patients with complex regional pain syndrome. Moreover, the perception of a smaller or larger body part can also be induced in healthy participants through proprioceptive illusions (Frederique de Vignemont, 2010) or through temporary peripheral proprioceptive deafferentation, which results in the affected body part feeling larger (Gandevia & Phegan, 1999). Damage to the central nervous also can affect body size perception. Macrosomatognosia is reported more frequently than microsomatognosia and is usually associated with parietal lesions (Frederiks, 1985). However, it has also been reported after a frontal lesion and in Parkinson's patients (Sandyk, 1998).

Body awareness disorders

Disorders in body awareness can arise at different levels. First, being aware of a physical deficit such as a paralysis can be disturbed. Different gradations exist, patients with anosognosia for hemiplegia reject the idea of physical impairment, while other patients admit the existence of their deficit but underestimate the severity and the implications of their physical impairment (anosodiaphoria). Anosognosia can exist for both motor and somatosensory impairments. The first is related to lesions to the posterior insula (Karnath, 2005), the second is a consequence of lesions to the basal ganglia (i.e. putamen) (Pia et al., 2014). Anosognosia for hemiplegia is relatively common with 18% of the first-ever stroke patients and 32% of the right hemisphere stroke patients suffering from this disorder (Appelros, Karlsson, Seiger, & Nydevik, 2002; Vocat, Staub, Stroppini, & Vuilleumier, 2010). A second group of disorders concerns impairments in awareness about (part) of the body itself. Patients with asomatognosia experience that a body part is 'missing' or has disappeared from corporal awareness. For example, the loss of awareness of one body-half (which may or may not be paralyzed). Another disorder related to disturbances in body ownership is somatoparaphrenia in which patients suffer from asomatognosia plus extensive delusions, misidentifications, and confabulations regarding the limb. For example, patients might give an alternative explanation for the limb disownership, for example by believing that the affected limb belongs to someone else, that is an animal or that it is part of a rotting corpse. A reverse interpretation has been observed as well, with patients identifying body parts of another person as their own (Gerstmann, 1942). Different theories on the etiology of asomatognosia and somatoparaphrenia exist, also because patients often suffer from other neuropsychological impairments. Therefore, hemispatial neglect, hemianesthesia, priopriceptive and attentional impairments have been commonly associated with asomatognosia and somatoparaphrenia (Feinberg, Venneri, Simone, Fan, & Northoff, 2010; Gandola et al., 2012; Vallar & Ronchi, 2009). Furthermore, it has been suggested that multisensory integration and building a spatial representation of the body is hampered (Vallar & Ronchi, 2009). Interestingly, these problems are only present for a first-person perspective, but diminishes when a patients views him or herself in the mirror (Fotopoulou et al., 2011). The duration of symptoms of asomatognosia and somatoparaphrenia varies from minutes to months. Interestingly, providing evidence to the patient that contradicts the delusion only temporarily reduces the denial, after which the asomatognosia or somatoparaphrenia returns. Misoplegia is a more affective form of body awareness disorder and can be defined as a hatred for the affected limb, with offensive behaviours toward the limb as a result. With respect to the underlying neural substrate, disorders of body awareness and ownership are often a consequence of large right hemispheric lesions, involving premotor, parietal and posterior insular areas (for review see (Vallar & Ronchi, 2009)). In addition, cases have been described in which somatoparaphrenic symptoms were induced through vestibular stimulation suggesting that body awareness disorders might be a consequence of functional rather that structural deficits (Ronchi et al., 2013).

Problems concerning body ownership and awareness can also occur when a limb is no longer a physical part of the body, as in the case of phantom limb phenomenon. This can be defined as “the persistent experience of the postural and motor aspects of a limb after its physical loss” (Brugger, 2005). Phantom limb experiences a present in approximately 95% of patients who undergo amputation of a limb (Melzack, 1990). A similar phenomenon (i.e. experience of a limb that is not physically present) can also occur after brain damage, but is less frequently observed. This is referred to as supernumerary phantom limb (SPL), and is defined as “the awareness of having an “extra limb” in addition to the regular set of two arms and two legs.” Multimodal experience of the extra limb has been reported including tactile (feel objects with their phantom arm), visual (visually perceive their phantom limb) and motor components (generate action), see Figure 4. Neural representations of this extra limb have been reported in the brain areas that represent these modalities, particularly in the left hemisphere (Khateb et al., 2009), although the phenomenon has been described after right-sided lesions as well (Miyazawa et al., 2004). Except for anosognosia, disorders of body awareness after brain damage appear to occur relatively infrequently, although it’s prevalence so far has not been well documented. They also tend to recover over time. These disorders are nevertheless of great interest as they can further our understanding of the functional and neural mechanisms underlying bodily awareness, body ownership and self-other distinctions.

Figure 4 | An example of the phantom limb phenomenon. A patient experiences a phantom hand but no forearm after amputation. *From: Wright Halligan and Kew, Wellcome SciArt Project 1997*

Conclusion

Central touch disorders can occur on multiple levels ranging from primary somatosensory perception disorders (e.g. a deficit in spatial acuity) to higher order disorders (e.g. shape detection, object recognition or body related disorders). These disorders can be present in absence of other deficits, although it is more common that they influence, and are influenced by other tactile and/or cognitive deficiencies. Compared to visual disorders, touch disorders receive less attention both in research as well as in clinical practice and their presence can therefore be underestimated. Nevertheless, they are linked to limitations in functional independence and therefore deserve more attention.

Chapter 3

The Rubber Hand Illusion in a patient with hand disownership

H.E. van Stralen
M.J.E. van Zandvoort
L.J. Kappelle
and
H.C. Dijkerman

As published in: Perception Vol 42, Issue 9, pp. 991-993, 2013.

H.E.S. and H.C.D. designed research; H.E.S. performed research and analyzed the data; H.E.S., M.J.E.Z L.J.K, and H.C.D. wrote the paper.

Abstract

A 78-year old patient with a sensory-motor ischemic stroke in the right hemisphere suffered from problems in ownership of her left arm (somatoparaphrenia). After recovering from motor weakness however, body ownership problems remained present. To assess whether disturbed feelings of ownership coincides with an enhanced or diminished susceptibility for gaining ownership over a foreign hand, we applied the “Rubber Hand Illusion” (RHI) to the ipsi- and contralesional hand. The RHI was significantly stronger for the contralesional arm than for the ipsilesional arm. In addition, solely visual exposure to the contralesional rubber hand was sufficient to elicit strong feelings of ownership over the rubber hand.

These findings suggest that disturbances in the feeling of body ownership allow a foreign hand to be incorporated more easily.

Introduction

Body ownership has been defined as the feeling that one's body belongs to oneself. Disruptions in this sense can result in an unawareness of one side of the body occasionally in co-occurrence with a delusional belief concerning the affected limb (somatoparaphrenia). That is, patients with somatoparaphrenia may believe that their own arm belongs to someone else (Vallar & Ronchi, 2009). This impairment has been reported in patients with acquired brain lesions, typically a large right hemispheric lesion. These types of lesion usually cause significant additional impairments in other neuropsychological functions and therefore limit experimental investigations of body ownership problems after stroke. Therefore, evidence remains inconclusive whether patients with somatoparaphrenia suffer from a general diminished sense of ownership, or that the demarcation between what belongs to their own body and someone else's body has been faded. In other words; is a sense of ownership per se impaired or is a patient more susceptible to gain ownership over a foreign hand?

Methods and Results

A 78-year old woman was admitted to the hospital with a clinical diagnosis of ischemic stroke in the right hemisphere. Initially she had left-sided sensory-motor deficits and suffered from problems in recognizing her left arm (i.e., she had a delusional belief that her arm was her fathers' arm). Within two weeks, she recovered from almost all acquired sensorimotor and cognitive impairments, as examined during a neuropsychological investigation. While the delusional belief largely receded, the patient remained confused about the ownership over her left hand. At this point, we conducted the Rubber Hand Illusion (RHI) (Matthew Botvinick & Cohen, 1998) to quantify the experience of ownership over a foreign hand. In this illusion, the patient is asked to place her forearms in a wooden framework with a movable board that occludes one of her arms (set-up adopted from (Kammers, de Vignemont, Verhagen, & Dijkerman, 2009) see Figure 1a. On each trial, the rubber arm and the invisible real arm are stroked for 90s, either synchronous or asynchronous. When in synchrony, the multisensory integration causes an experience that the touch applied to the rubber hand as if it is applied to the own hand, suggesting a sense of ownership over the rubber hand. A 2×2 design was used, i.e. two stroking condition (synchronous or asynchronous), and two hand sides (left or right) and each trial was measured for four times, 16 in total. After each trial, three different outcome measures were obtained. First, the felt location of the own (stimulated) hand was obtained and the deviation with the actual position was calculated, known as the proprioceptive drift. This displacement towards the rubber hand can be used as a measure to assess the occurrence and also the strength of the subjective feeling to own the rubber hand.

A two-factor (synchronicity and side of stimulation) ANOVA revealed a significant main effect for hand side $F(1,12)=39.72$, $p<.01$ with a larger proprioceptive drift towards the rubber hand when the left hand was stimulated as opposed to the right hand (mean difference 8.5 centimeter). See Figure 1B. For the left hand, the proprioceptive displacement was also present during asynchronous stroking, but not for the right hand. An interaction effect between synchronicity and side of stimulation reached the significance level $F(1,12)=6.76$, $p<.05$, of which the proprioceptive drift of the left hand in the asynchronous condition contributes largely to this effect. This suggest that the asynchronous condition reinforced the illusion rather than serving as a control condition, possibly due to the patients' perception of additional stimulations on the arm[1].

Second, the temperature of the skin of both hands before and after each stimulation trial was measured (Raytek handheld Autopro (ST25) laser thermometer) and the difference between those measurements was calculated. A temperature drop is considered as an objective measure of body disownership (Moseley et al., 2008). A two-factor (synchronicity and measurement-stimulation congruency) ANOVA revealed a significant main effect of the side where the RHI was conducted, $F(1,24)=5.94$, $p<.05$. See Figure 1C. Specifically, stroking on the left hand resulted in a larger temperature drop for the left hand compared to stroking of the right hand (mean difference .85°C SE.26). Also, during left hand stimulation, there was no drop in temperature of the right hand suggesting that the temperature drop was specific for the left hand rather than a physical response in general. Third, a subjective illusion was quantified by means of a questionnaire that consists of both statements related to the illusion and statements that are considered as control items. Results show that the patient rated higher scores on the illusion related statements for the left (affected) hand compared to the right hand as measured with a paired sample t-test $t(7)=2.52$, $p<0.05$. See Figure 1 D. In addition, the patient reported a strong illusion during asynchronous stroking for the left hand, but not when the right hand was stimulated. The patient reported maximum scores on the illusion-related questions but not on the questions that serve as a control, suggesting a genuine response on the illusion rather than task compliance or a general susceptibility.

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[1] The patient also reported a vivid illusion for the left hand (and not for the right) during asynchronous stimulation. In both stroking conditions, she reported as if the rubber arm and her own arm felt "identical and as if they were one". For the asynchronous condition, the patient reported that the discrepancy between the visual and tactile stimulation resulted in the feeling that the tactile stimulation 'felt as an echo'. The patient 'felt' the visual stroking on the rubber hand. In addition, the tactile stimulation on her real hand was experienced as if it was coming from the rubber hand, also known as vision-touch synaesthesia (Aimola Davies & White, 2013). On a speculative account, the perception of these added stimulation may have contributed to the high scores on the proprioceptive drift as well as the subjective illusion.

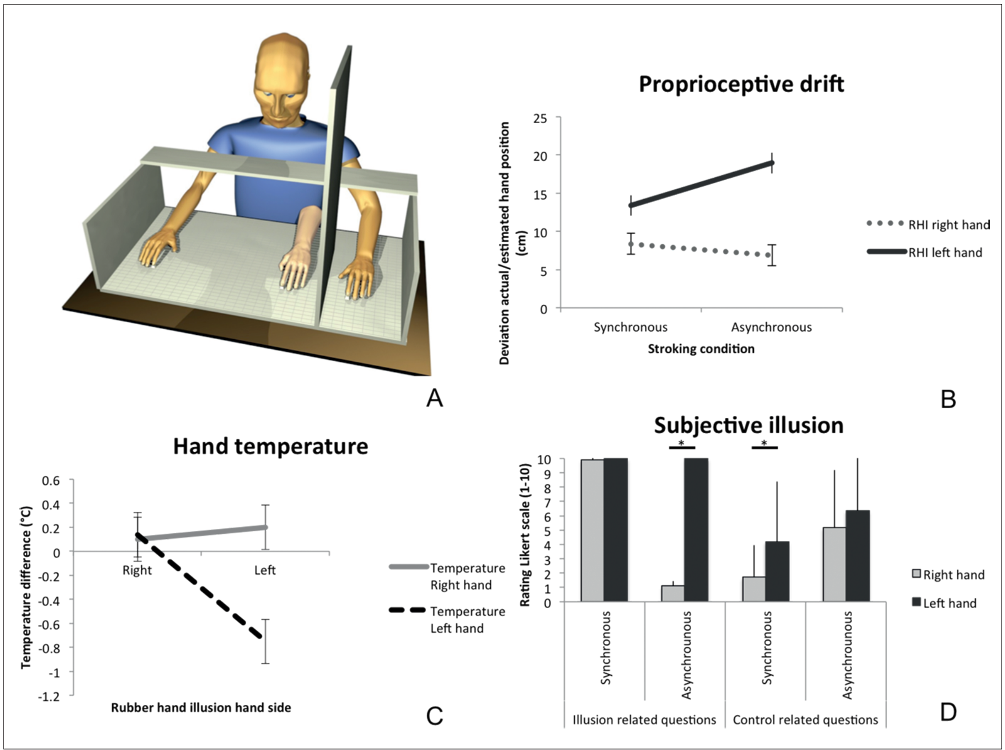

Figure 1 | a): Experimental set-up of the Rubber Hand Illusion. b): The proprioceptive drift. Scores represent the deviation between the actual hand position and the estimated hand position. c): The hand temperature. Scores represent the difference between the temperature before and after RHI induction. d): The subjective illusion. The illusion-related statements (averaged rating of statements 1-3) and the control statements (averaged ratings statements 4-10) for the synchronous and asynchronous condition.

Discussion

In sum, for all three outcome measures, a stronger illusion for the contralesional hand compared to the normal right hand was observed. In addition, body ownership deficits were so profound that, when compared with synchronous stroking, asynchronous stroking of the left arm induced a RHI of similar (subjective experience) of even of larger (proprioceptive drift) magnitude. This suggests that the visual capture of the left rubber hand was sufficient to induce the RHI.

With this study, we were able to objectify (i.e., proprioceptive drift and temperature drop) subjective reports of body ownership problems. The results show that deficits in body ownership results in an increased experience of ownership over a foreign hand. This suggests that a weakened innate sense of ownership allows space to gain ownership over a foreign hand more easily. On a speculative account, body ownership deficits obliges a patient to rely more on sensory input to determine what belongs to the bodily self. As a consequence, modifying the sensory input increases the susceptibility for the illusion. These exciting findings warrant replication in a large sample of patients with ownership deficits.

Chapter 4

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

H.E. van Stralen*
M. Smit*
B. van den Munckhof
T.J. Snijders
and
H.C. Dijkerman

In press: Journal of Neuropsychology, 2018

H.E.S., M.S. and H.C.D. designed research; M.S., and H.E.S collected the data; M.S. analysed the data; H.E.S., M.S., B.M., T.J.S., and H.C.D. wrote the paper.
* H.E.S. and M.S. contributed equally.

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 tumour resection in the right temporoparietal 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 (Baier & Karnath, 2005; Gandola et al., 2012; Nightingale, 1982; Vallar & Ronchi, 2009) suggested that disownership of limbs in patients with somatoparaphrenia (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, de Vignemont, et al., 2009) and the ventral premotor cortex (H. Ehrsson, 2005; Zeller, Gross, Bartsch, Johansen-Berg, & Classen, 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.

Methods and Results

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 (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.

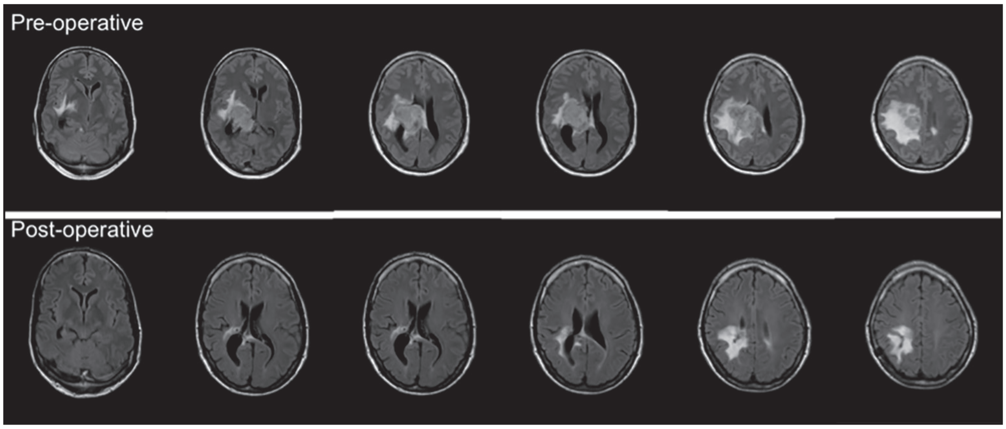

Figure 1 | MRI scans with T2-weighted images with fluid attenuated inversion recovery (Flair) in axial plane. The upper row represents pre-operative images showing a circumscript right intraventricular lesion with dimensions 5×4×4 centimeters (with T1 enhancement).

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 diminishes 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

SA underwent two examinations 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 1.

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 (VAS)	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 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 (Winward, Halligan, & Wade, 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 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 (hand) 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[1] 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 & 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 measure were not administered during the first session.
*** significantly different from controls (p<.0001)

In addition, we presented the classic RHI (see (Matthew Botvinick & Cohen, 1998) for a detailed procedure; set-up adopted from (Kammers, de Vignemont, et al., 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 arm are stroked for 90 seconds, either synchronously or asynchronously. Commonly, the synchronous visuotactile stimulation causes highest feelings of ownership (Matthew 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 (Ferri, Costantini, Chiarelli, Merla, & Gallese, n.d.; Longo, Schüür, Kammers, Tsakiris, & Haggard, 2008). Asynchronous stimulation would result in the least illusion and usually serves as a control condition. Indeed this is

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

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. (behavioral) 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, de Vignemont, 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 3×5 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 (see 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 found an ‘ownership’ drop 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

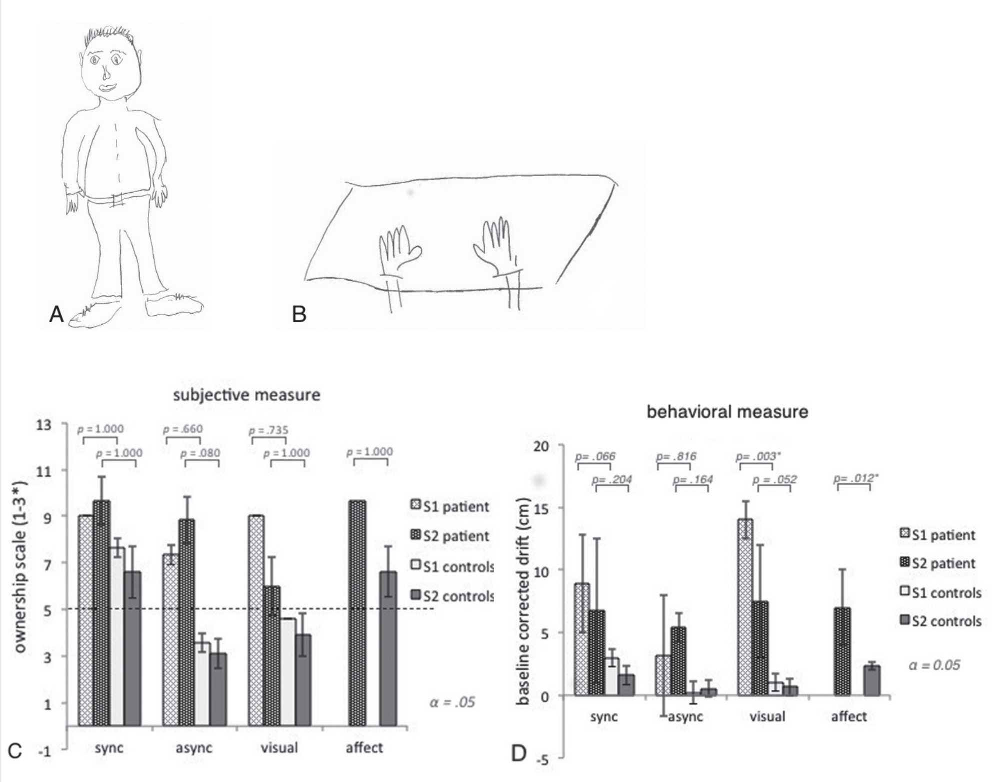

Figure 2 | A): Left panel: drawing of a physical human body and (right panel) drawing of own experienced body. When instructed to draw a person, he drew an appropriately sized body with correctly attached limbs, indicating intact semantic knowledge of the configural layout of a human body. However, when instructed to draw the experienced own physical body, he initially hesitated and needed further encouragement. SA reported that he was not able 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 B). What is particularly striking is that this drawing is indicative of the reports of the patient. When 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. C): 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 C 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. D): Average baseline corrected (post – pre-session) proprioceptive drift (in cm) for all conditions for the left hand for SA and controls.

control participant. Statistically, results resembled the first session (Figure 2C, D), except that the visual condition was near significant between the controls and the patient. Additionally, we added a slow stroking (range of 1–10cm/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 (Crucianelli, Metcalf, Fotopoulou, & Jenkinson, 2013; Van Stralen et al., 2014). During this condition, both measurements (Figure 2D, E), 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 2C, 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 this condition only for SA.

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 were 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 (Burin et al., 2015; Llorens et al., 2017; van Stralen, van Zandvoort, & Dijkerman, 2011; White & Aimola Davies, 2017; Zeller et al., 2011). 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, van Zandvoort, Kappelle, & Dijkerman, 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 (van Stralen et al., 2013; White & Aimola Davies, 2017). 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 and colleagues (White & Aimola Davies, 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 (Stein & Stanford, 2008; Tsakiris, 2010) 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 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 of neuropsychological examination 5 months after tumor resection.

Test	Percentile/score*
Cognitive Screening test	
Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975)	29/30
Language	
Boston naming task (Kaplan, Goodglass, & Weintraub, 2001)	80th percentile (Heesbeen, 2001)
Word Fluency (Benton, 1968)	80th percentile (Schmand, Groenink, & van den Dungen, 2008)
Working memory	
Digit span(WAIS-III) (Weschler, 2008)the Wechsler Adult Intelligence Scale \u2013Fourth Edition (WAIS-IV	41st percentile
Corsi Block tapping Test (Corsi, 1973)	10-20st percentile (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000)
Memory	
Rey Auditory Verbal Learning Test (Rey, 1958; van der Elst, van Boxtel, van Breukelen, & Jolles, 2005)	
immediate recall	69th percentile
delayed recall	54th percentile
recognition	30/30 qualified as not impaired
Location Learning Test (Kessels, Nys, Brands, van den Berg, & Van Zandvoort, 2006)	
immediate recall	40th -50th percentile
learning index	60th -70th percentile
delayed recall	30th -85th percentile
Rivermead Behavioral Memory Test (Schmand, Houx, & de Koning, 2004; Wilson, Cockburn, & Baddeley, 1985)	
story immediate recall	16th percentile
story delayed	4th percentile
Visual perception	
Benton Judgment of Line Orientation(Benton, 1983)	>86th percentile
Benton Facial recognition test (De Renzi, Faglioni, & Spinnler, 1968)	88th -97th percentile
Schenkenberg Line Bisection (Schenkenberg, Bradford, & Ajax, 1980)	average -2.75 deviation (left) (qualified as not aberrant)
Cortical Vision Screening (James, Plant, & Warrington, 2001)	69/70 (qualified as not impaired)
Facial expression of Emotion (Ekman, 1993)	32/36 (qualified as not impaired)
Stereognosis (object/drawing)	8/8 (qualified as not impaired)

Table 1 | *(Continued)*

Tactile pointing	Left, 2 cm, right 1.9 cm (qualified as not impaired)
Finger gnosis (van Stralen et al., 2017)	
Virtual Reality Tubingen (Claessen, van der Ham, Jagersma, & Visser-Meily, 2016)	
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 (Ofte, 2002)	144/144 (qualified as not impaired)
Goldenberg ideomotor Apraxia (Goldenberg, 1995, 1996)\	20/20 (qualified as not impaired)
Speed processing	
Trail Making Test A (Tombaugh, 2004)	73rd percentile
Trail Making Test B	79th percentile
Stroop colour-word-test (Golden, 1976; Schmand et al., 2004)	
card I,II,III	38th, 50th, 96th percentile
Executive functioning	
The Hayling and Brixton test (Burgess & Shallice, 1997)	99th percentile
Behavioral Assessment of dysexecutive Syndrome (Wilson et al. 1996)	
key search	Profile score 3 (qualified as not impaired)
zoo map	Profile score 2 (qualified as not impaired)

Chapter 5

The role of self-touch in somatosensory and body representation disorders after stroke

H.E. van Stralen
M.J.E. van Zandvoort
H.C. Dijkerman

Based on: The role of self-touch in somatosensory and body representation disorders after stroke, 2011. Philosophical Transactions of the Royal Society of London B: Biological Sciences, 366(1581), 3142-52.

H.E.S., M.J.E.Z., and H.C.D. designed research and wrote the paper. H.E.S. and H.C.D. collected the data. H.E.S. analyzed the data.

Abstract

Somatosensory impairments occur in about half of cases of stroke. These impairments range from primary deficits in tactile detection and the perception of features, to higher order impairments in haptic object recognition and bodily experience. In this paper, we review the influence of active- and self-touch on somatosensory impairments after stroke. Studies have shown that self-touch improves tactile detection in patients with primary tactile deficits. A small number of studies concerned with the effect of self-touch on bodily experience in healthy individuals have demonstrated self-touch influences the structural representation of one's own body. In order to better understand the effect of self-touch on body representations we present an informal study of a stroke patient with somatoparaphrenia and misoplegia. The role of self-touch on body ownership was investigated by asking the patient to stroke the impaired left hand and foreign hands. The patient reported ownership and a change in affect over all presented hands through self-touch. The time it took to accomplish ownership varied, based on the resemblance of the foreign hand to the patient's own hand. Our findings suggest that self-touch can modulate impairments in body ownership and affect, perhaps by helping reinstate the representation of the body.

Introduction

Deficits in somatosensory function after stroke are relatively common, occurring in about half of the patients (Carey, 1995). They are not a unitary phenomenon and impairments range from deficits in basic detection and in perception of features such as shape and texture, to tactile agnosia and body disownership. In this review we will describe these impairments and particularly discuss the role of active touch in these deficits. The somatosensory system involves serial as well as parallel processing of sensory input and this is reflected in the deficits observed after stroke (Bohlhalter et al., 2002; Dijkerman & de Haan, 2007). Serial processing can be found in terms of deficits in primary somatosensory deficits that affect higher order functions such as haptic object recognition. At the same time the presence of selective deficits in for example haptic object recognition with intact recognition of body parts by touch suggests a parallel organisation. In this review the role of active self-touch in modulating somatosensory deficits after stroke is discussed. Several studies have shown that self-touch improves perceptual detection for the affected body parts. The circumstances in which this occurs and the underlying mechanisms are discussed. In the final section, a case study of a stroke patient with impairments in bodily experience is described. In this patient the role of self-touch on body ownership was systematically investigated and the possible underlying mechanisms are discussed.

Self-touch and somatosensory functioning

Accumulating evidence shows that actively touching one's own body may involve different sensory mechanisms compared to being touched passively. The different mechanisms underlying self-touch and touch by others have been observed both in healthy individuals (Blakemore, Frith, & Wolpert, 1999; Weiskrantz & Zhang, 1987) and in patients with somatosensory deficits. In this section, we review the literature on self-touch and elementary tactile deficits after stroke. Furthermore, we will present a case study in which self-touch modulated higher order processes, that is, ownership over her affected arm.

Self-touch and tactile perception

Self-touch enhancement

The effect of active self-touch in modulating somatosensory perception after stroke was first reported by Weiskrantz and Zhang (Weiskrantz & Zhang, 1987). A right hemispheric stroke patient with clear sensory deficits in the contralesional hand who was unable to detect tactile stimulation administered by the experimenter was described. In contrast, the patient was able to feel tactile stimulation on the affected hand when it was touched by the own unaffected hand or by a probe that was held by this hand. Thus, tactile sensitivity was enhanced by active self-touch. This finding was replicated more recently in a larger sample of stroke patients in which 22 out of 39 patients showed self-touch enhancement (Valentini, Kischka, & Halligan, 2008). Most of the patients with enhanced self-touch (17/22) suffered right hemisphere lesions. The mechanisms underlying the self-touch modulation have not yet been established, although several mechanisms have been proposed. These include i) a heightened attention towards the spatial region of the affected hand ii) the use of proprioceptive information of the administering hand and iii) the use of predicted sensory consequences of the generated action.

The influence of attention on somatosensory perception has been widely investigated in healthy individuals. Several studies have focused on how visual attention modulates somatosensory perception. They showed that orienting the eyes toward a body part facilitates detection of touch, which could not be explained by proprioceptive information or visual information of the target (Larmande & Cambier, 1981). In addition, other studies showed that tactile extinction diminished when a visual stimulus was presented close to the affected hand (Làdavas, di Pellegrino, Farnè, & Zeloni, 1998). Besides directing visual attention, other studies demonstrated that non-visual attention also changes perceptual processing. For example, Coslett and Lie described two patients who suffered from tactile extinction as a result of a right hemispheric brain lesion (Coslett & Lie, 2004). The ability to detect tactile stimulation with the affected hand improved by direct passive skin contact with the ipsilesional hand. It was suggested that the unaffected hand provided a focus of attention to the extinguished side.

Another contributing factor to self-touch modulation in patients is the use of proprioceptive information, which provides the patient with information about whether the administering hand is close to the affected hand and is touching it. Studies on healthy participants have demonstrated the interaction between touch and proprioception with the so-called Pinocchio illusion. This illusion is obtained when the passive biceps tendon is vibrated while participants hold the tip of the nose between finger and thumb. As a result of this stimulation, a proprioceptive illusion is induced in which the elbow extends and the nose elongates (Kammers, van der Ham, & Dijkerman, 2006; Lackner, 1988; Ramachandran & Hirstein, 1998). The role of proprioception in tactile enhancement is investigated with experiments in which proprioceptive input is non informative during detection of touch. For example, Valentini et al. (Valentini et al., 2008) and Weiskrantz & Zhang (Weiskrantz & Zhang, 1987) controlled the proprioceptive input by having the patient's affected hand interdigitated with the examiner's hand. Sometimes the patient would touch their own affected hand; in other trials the experimenter's fingers were touched. Self-touch enhancement was reliably observed only when their own affected hand was touched, suggesting that proprioception is not the primary contributor to self-touch. In line with this result, White et al. (White et al., 2010) stated that neither proprioceptive information nor attention towards the spatial region of the affected hand offers a sufficient explanation for self-touch enhancement. Instead, they showed that a temporal delay between administration and actual tactile stimulation eliminated the self-touch enhancement, suggesting an important role for temporal expectation. Thus action with the administering hand provides a precise temporal cue for focusing attention on the affected hand.

Self-touch attenuation

Although some studies show that self-touch increases the sensitivity for tactile stimulation, other studies report attenuation for tactile stimulation during self-administered touch. For example, researches have investigated the issue of 'why we can't tickle ourselves' and concluded that self-generated action diminishes the intensity of the tactile stimulation that accompanies the action (Blakemore et al., 1999; Weiskrantz, Elliott, & Darlington, 1971). These findings are in concordance with the 'forward model' that is thought to make a prediction about the sensory consequences of an action (Jordan et al., 1992; Sperry, 1950; Wolpert & Miall, 1996). This prediction allows self-produced stimuli to be attenuated, giving the opportunity to signal more an external event that provides information that is novel. Jackson et al. (Jackson, Parkinson, Pears, & Nam, 2011) demonstrated in an fMRI study that a somatosensory stimulus delivered to a hand that is being prepared for movement is perceived later than when the same stimulus is delivered to a stationary hand for which no movement is prepared. In addition, during stimulation on the hand prepared for motion, reduced activation was observed within the bilateral parietal operculum and insula compared to the non-moving hand. The authors interpreted the perceived delay as a result of an increased somatosensory threshold.

Thus self-touch has been associated with both enhanced and reduced tactile sensitivity. The discrepancy between self-touch enhancement and the self-touch attenuation is as yet not explained. Jackson et al. (Jackson et al., 2011) pointed out that the two different theories, i.e. the attenuation of tactile perception by the forward model and the enhancement of tactile perception by attention, might in fact be consistent with each other. The estimate of the sensory consequences of a self-generated action is largely irrelevant to behaviour and therefore, attenuation of these stimuli may be beneficial to monitor other signals. White et al. (White et al., 2010) proposed that an accurate temporal anticipation is the crucial factor underlying self-touch enhancement, allowing enhancement of processing resources for the anticipated stimulus.

Self-touch and body representation

Although there is considerable evidence for modulation of tactile perception by self-touch, less is known about self-touch modulation and higher order somatosensory processing. A recent report demonstrated a right-hemispheric stroke patient who was able to detect somatosensory stimulation on the left hand but was not able to localise the stimulus (White et al., 2010). This suggests that the patient had an impaired representation of the affected hand. Interestingly, localisation on the affected hand improved when the patient reached with the right hand to the left of the own affected hand while having the illusion of self-touch. The authors hypothesised that self-touch might have altered the patients' representation of the affected hand. The effect of self-touch on the structural body representation is also investigated in a study with healthy individuals (Schütz-Bosbach, Musil, & Haggard, 2009). In this elegant experiment, subjects were asked to touch several fingers of one hand with fingers of the other hand. They induced a discrepancy between the number of fingers touched on the active and on the passive hand by interleaving the experimenter's fingers between the fingers of the passive hand. When asked to name the number of fingers in between fingers, participants showed an underestimation that was specific for the self-touch conditions. This suggests that self-touch influences the structural representation of one's own body. In a recent study, Kammers and colleagues investigated the influence of touch on paradoxical pain using the thermal grill illusion (Kammers, De Vignemont, & Haggard, 2010). They induced the thermal grill illusion by placing the participant's index and ring finger in hot water and the middle finger in cold water. This results in paradoxical feeling of painful heat in the middle finger. It was shown that the painful heat induced by the illusion was reduced when the fingers of the other hand touched the fingers used to induce the illusion. They suggested that this self-touch effect is not due to low-level touch temperature interactions, but that an increase in the coherence of body representations is involved.

These reports have provided accumulating evidence that self-touch has more extensive representational effects rather than the sensory-attentional enhancement reported previously (Valentini et al., 2008). Although they demonstrated that self-touch modulates body representation in healthy participants, the question remains whether self-touch can be beneficial for patients who suffer from body representation impairments. While the White et al. study (White et al., 2010) suggests that self-touch can enhance tactile localisation, so far, the effects of self-touch on bodily awareness and body ownership disorders have not been reported. Here we describe an informal case study in which we investigate the effect of self-touch on body representation.

Self-touch and disorders in body representation

Case history and observation

Patient GE is a 60-year-old woman who had a large right intra-axial hemorrhagic stroke affecting the right parietal and frontal lobes (see Figure 1). As a consequence she suffered from left hemiplegia, hemianaesthesia and left hemispatial neglect. There was evidence of anosognosia for hemiplegia. Moreover, GE reported that she had problems in identifying her left hand and arm as her own. The hospital staff also noticed that GE occasionally mistook the hand of someone else for her own (somatoparaphrenia). GE reported that she had experienced negative feelings toward her left arm (misoplegia) since her stroke. These included the feeling of hatred and the urge to harm or punish the arm. These negative feelings were no longer present at the time of assessment two weeks later. A striking observation was that the patient was stroking her left arm and hand affectively. GE reported that this was because she felt the stroking in the affected hand and this helped her to regard the arm as a part of herself.

GE was assessed two weeks after her stroke. Her speech was fluent and informative. She was able to understand questions and instructions and was motivated to cooperate with the investigations. A neuropsychological assessment revealed impairments in several cognitive domains, including long-term memory, working memory, visual perception, visuoconstruction and executive functioning. Furthermore, the patient demonstrated finger agnosia, proprioceptive impairments and astereognosis. In addition, evidence for peripersonal neglect was found. Besides these impairments, GE was oriented in person, place and time. Also, her attention span was unimpaired. At the time of the assessment, GE did not report problems regarding the sense of ownership or the affect for her contralesional limbs.

GE was not able to detect somatosensory input on the left side of her body when the experimenter administered it. However, the patient reported the sense of touch in her contralesional hand when the right ipsilesional hand generated the touch (self-touch). Interestingly, this was regardless of whether she perceived direct skin contact with her ipsilesional hand since she felt the touch as well when her ipsilesional hand administered touch by a paintbrush. This observation is consistent with the idea that temporal expectation is an important mechanism for self-touch enhancement (White et al., 2010).

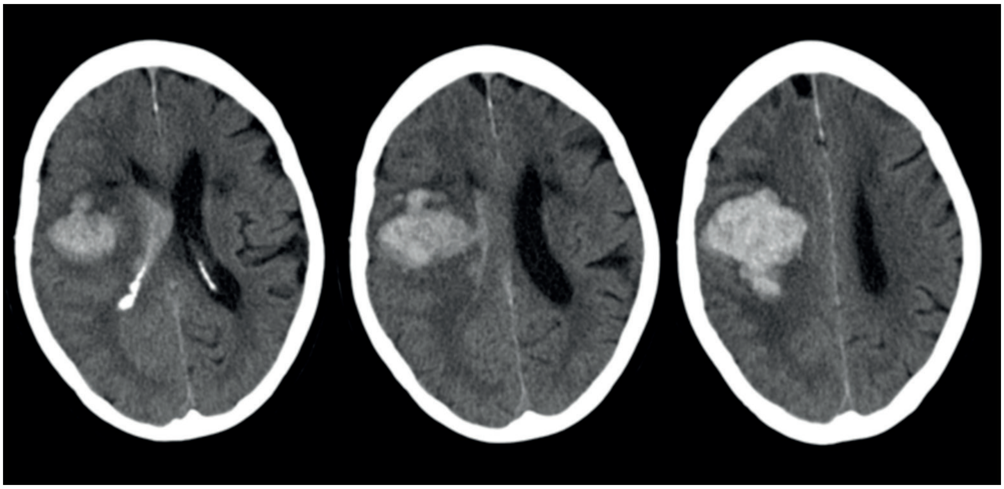

Figure 1 | Three images of an axial plane CT-scan of patient GE showing a large hemorrhagic stroke in the right hemisphere. The images follow the radiologist convention of right hemisphere represented on the left.

Hypothesis I: Active (self-)touch enhances ownership

Our main investigation aimed to test whether the self-touch could have helped the patient in ‘keeping the arm as a part of herself’ as she spontaneously suggested. In other words, does self-touch affects disorders of body ownership? To investigate this, GE was asked to stroke her own arm and different arms that were not her own, referred to as foreign arms. For the experimental design and set-up, see Figure 2a and b. The following foreign arms were used: I) a left rubber arm II) the left arm of the experimenter III) a right rubber arm IV) a left rubber arm in an anatomically implausible position. GE was asked to stroke the dorsal surface of the arm (own arm or foreign arm) for three minutes, and to comment on the arm that she was stroking. In particular, she was asked whether she thought the stroked arm belonged to her or someone else. The time it took to report ownership over the arms was recorded. Immediately after the first stroke and three minutes after stroking, she was asked to rate the emotional valence towards her arm, ranging from 0 (=negative) to 5 (=excessive positive emotional valence). First GE stroked her own arm for 3 minutes and after the emotional valence rating GE started to stroke the first foreign arm (i.e. the left rubber arm) followed by the emotional valence rating. The conditions ‘own arm’ and ‘foreign arm’ alternated four times.

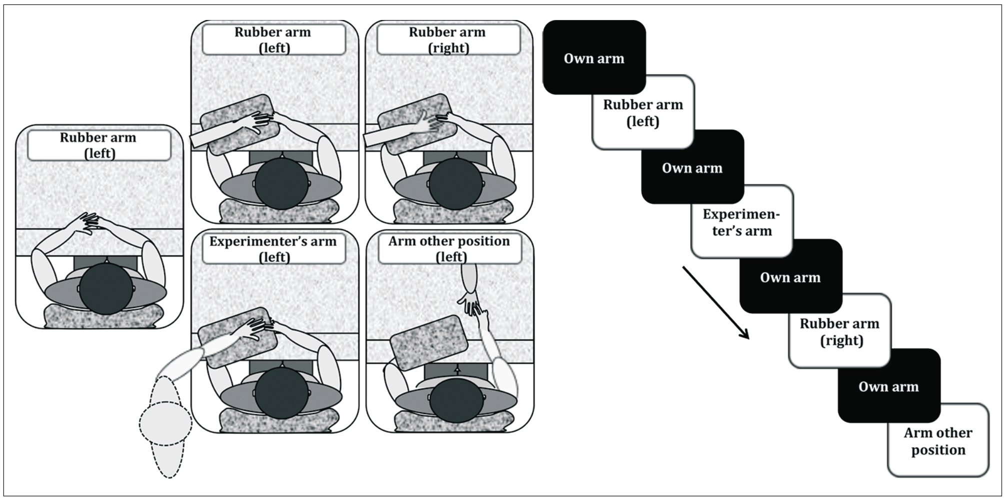

Figure 2a and b | Experimental design. a):The patient stroked different arms alternating her own arm and foreign arms. The stroking time for each arm (own arm and foreign arms) was three minutes. Within the three minutes, the time it took to achieve ownership over the arm was recorded. b): Experimental set-up. The patient was asked to stroke the dorsal surface of her own hand. During stroking of the foreign arms, the position of the own arm remained unchanged, except that a pillow covered the own arm. The foreign arms were positioned similar to the own arm except that they were positioned on top of the pillow. The foreign arms in the anatomical implausible position did not match the position of the own arm. While stroking, the patient was asked whether she thought the stroked arm belonged to her or to someone else.

Stroking of the arms resulted in an increased sense of ownership over the particular arm. More specifically, GE reported a sense of ownership over all four foreign arms by stroking. Interestingly, during stroking, her attitude toward the arm changed noticeably from a dislike and rejection toward a more affective stroking and increasing belief that the foreign arm was a part of her body. Although the patient achieved the sense of ownership over all the foreign arms, the stroking time that was needed to achieve the sense of ownership varied between the different arms. This variation possibly depended on the level of similarities between the real arm of the patient and the foreign arm, see Figure 3. For example, to achieve a sense of ownership over the experimenter's arm the stroking time that was needed was 15 seconds, whereas 125 seconds of stroking was needed to achieve a sense of ownership over a right rubber arm. This suggests a top-down component in which a structural representation of her own arm influences the tendency to regard another arm as belonging to her. In healthy individuals, somewhat similar top-down influences have been observed when inducing the rubber hand illusion (RHI) (83). However, while the RHI induction fails when a right rubber arm is stroked synchronously with a left real arm, or when the rubber arm was placed in an anatomically incongruent condition, in the current case study ownership over the rubber arm was eventually achieved. These results confirmed our hypothesis that active (self-)touch indeed enhances ownership.

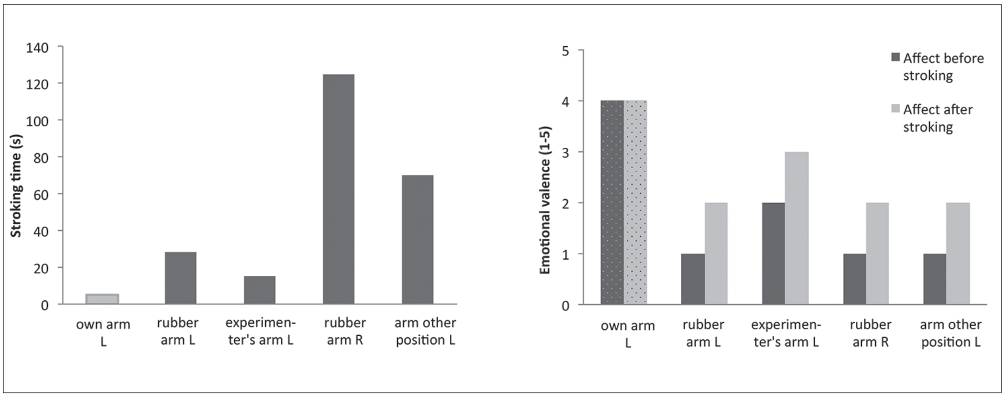

Figure 3a and b | The effect of stroking condition on the time needed to obtain ownership. a:) The results show that the stroking time that was needed to achieve the sense of ownership varied, based on the level of similarities between the real arm of the patient and the foreign arm. Note that the stroking time for the foreign arms was recorded once, whereas the stroking time for the patient's own arm is an average of four trials. b:) The effect of stroking condition on affect towards hand before and after obtaining ownership. For all arms, the affect (determined by VAS for emotional valence) increased during stroking of the foreign arms. The experimenter's arm is rated higher in positive valence; probably because this arm has a greater resemblance with the patient's own arm than the other arms. Note that the scores for the foreign arms were recorded once, whereas the scores for the patient's own arm is an average of four trials.

Another result of this investigation was the change in affect toward the arms. For all arms, the affect increased during stroking of the foreign arms, see Figure 3b. However, similar to the time differences in achieving ownership, the level of affection seems related to the resemblance to the structural aspects of her own arm. For example, the emotional valence toward the experimenter's arm is more positive compared to other foreign arms. In addition, the positive valence toward her own real arm was highest and similar to the emotional valence GE reported about her other limbs. The positive valence toward her own real arm did not differ between the first stroke and after three minutes. Intriguingly, when we showed the patient her own arm after stroking a foreign arm, she did not visually recognize this arm as her own and regarded her arm as unpleasant. However, when she touched her own arm with her ipsilesional hand she immediately acknowledged that the arm she was holding was hers, which coincided with a positive affect. This suggests that although ownership over her own affected arm was weakened and therefore could be extinguished by stroking a different arm (active touch), merely touching the affected arm reinstated ownership and re-established normal positive affect appreciation. This observation also suggests that stroking a foreign arm is followed by a sense of disownership of her real arm. To investigate this further, a second investigation was conducted.

Table 1 | Questions asked to rate the degree of presence (scale 1-4) of different deficits in body ownership. Certain ratings are reversed for clarification.

deficits	question	1	2	3	4
change in affect	are you as content with your arm as you used to?	yes			no
misoplegia	do you have a tendency to harm your arm?	no			yes
anosognosia for hemiplegia	are you able to move your left arm?	no			yes
asomatognosia	does this arm [pointing to hemiplegic arm] belong to you?	yes			no
somatoparaphrenia	does this arm [pointing to hemiplegic arm] belong to the experimenter?	no			yes

Hypothesis II: Stroking a foreign arm disowns the real arm

The second investigation aimed to assess whether stroking a different arm caused disownership of her real arm as was suggested by the first investigation. In addition, we wanted to ascertain that stroking the affected hand only induced changes in ownership when performed by herself rather than by someone else, the differentiation between self touch and active self-touch.

Three stroking conditions were used: I) Stroking her contralesional hand with her ipsilesional hand (active self-touch) II) Stroking her contralesional hand by the experimenter (passive self-touch) III) Stroking a left rubber arm by her ipsilesional hand (active touch). These stroking conditions were administered three times each, for duration of 90 seconds. The conditions were administered in a randomized counterbalanced order. After each condition, five questions were administered to assess whether different possible deficits regarding her hemiplegic hand were present, see Table 1. The five questions aimed to target signs of five different deficits, i.e.: change in affect, misoplegia, anosognosia for hemiplegia, asomatognosia and somatoparaphrenia. The questions targeting these deficits could be answered by a 4-point scale, ranging from 1=not present to 4=present.

The results showed that after GE stroked a rubber arm (active touch), there were clear changes in affect towards her own arm (see Figure 4). In addition, she showed signs of asomatognosia by rejecting her own arm as belonging to her body. These changes did not occur when she had stroked her own arm (active self-touch), or when the experimenter had stroked her arm (self-touch). As expected based on the previous observations, GE reported she did not feel the stroking when the experimenter stroked her arm, whereas she reported that she did feel the stroking in her contralesional arm when she was the agent of the stroking. The findings of changes in affect and ownership over her own arm following the stroking of the rubber arm indicates that stroking a rubber arm induces deficits in the sense of ownership over her real arm. Possibly, GE obtained an enhanced sense of ownership over the rubber arm by stroking, similar to the first experiment. As hypothesised in the first experiment, stroking helped her with re-establishing the representation of her arm. However, with stroking a rubber arm the representation that is build differs from the representation of her real arm. As a result, her real arm does not match with the newly build representation and is therefore rejected. As hypothesised, these results suggest that ownership over a rubber arm disowns the real arm.

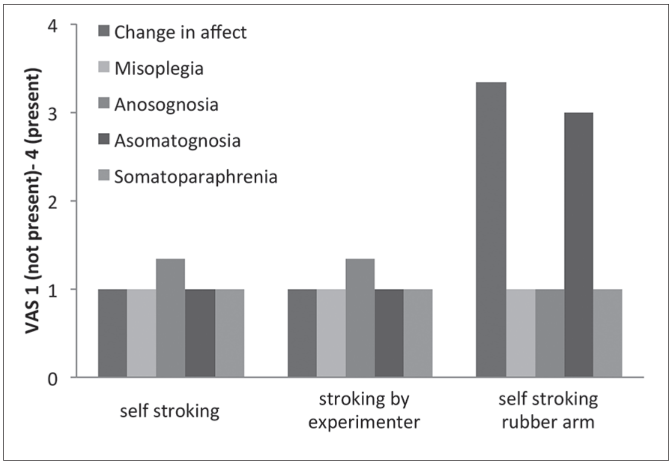

Figure 4 | Effect of stroking condition on the sense of ownership of the affected arm. The stroking conditions comprised: I) Self-stroking: The patient stroked her contralesional hand with her ipsilesional hand. II) Stroking by experimenter. The experimenter stroked the contralesional hand of the patient. III) Self-stroking a rubber arm. The patient stroked a left rubber hand with her right (ipsilesional) hand. The results show the mean scores (3 trials) on the questionnaires.

Limitations

Before we draw conclusions from these investigations, several limitations need to be considered. Similar to other patients with body ownership disorders, GE's hemorrhagic stroke affected several cognitive domains and resulted in increased fatigue. GE suffered from deficits in long-term memory, working memory, visual perception, visuoconstruction and executive functioning. One could assume that these cognitive deficits resulted in an overall confusion that caused the changes in the attitude towards her arm. However, her attention span as well as her orientation to place, time and person was unimpaired, preserving the ability to direct and hold her attention towards the investigations. Furthermore, an overall fatigue or confusion could not explain the differences in stroking time that was needed to achieve ownership (hypothesis 1).

Another limitation of the current study is that the sense of ownership was measured by verbal response of GE, and therefore, an objective measure of ownership is missing. As a result, the possibility cannot be ruled out that the patient had a tendency to comply with the expectation of the experimenter and reported having a sense of ownership over a foreign arm when this was not the case. However, besides verbal response, a change in the attitude of GE was also observed. For all foreign arms, the patient was reluctant to stroke the foreign arm at first. Her attitude towards the arms changed from rejection to more affective -almost cuddling- stroking of the foreign arm. In addition, again the variation in stroking time between the different arms suggests that her response reflects a reliable sense of ownership rather than a random tendency to accept every arm as her own. Nevertheless, to rule out these uncertainties and to test our newly raised hypotheses, more controlled trials are required. A more fundamental point of criticism that we have to take into account is whether the body ownership problems of the patient might have interfered with the questions we asked about her own arm. As hypothesised, the patient achieved a sense of ownership over the rubber arm after stroking. If this hypothesis were true, how do we know for certain that the questions we asked about her real arm were not conceived as questions about the rubber arm? The changes in affect and sense of ownership would therefore concern the rubber arm, instead of her own arm. This would be in line with the findings of the first experiment, in which a less positive affect for the rubber arm compared to her own arm is found. For future research, it would be interesting to investigate whether a newly achieved sense of ownership automatically results in a sense of disownership of the own limb, as implied by the second investigation.

Discussion

The overall aim of the current paper was to review the role of active and self-touch on the variety of somatosensory deficits ranging from elementary, primary deficits to impairments in the bodily experience. Most studies on self-touch have focused on primary tactile perception, and demonstrated changes in the detection threshold as a result of self-touch in patients with primary somatosensory deficits. Recently, a few studies have also demonstrated changes in the structural and cognitive aspects of body representation following self-touch in healthy-participants (80). The current study extends the knowledge of the effect of self-touch by demonstrating the role of self-touch on bodily experience. It was shown that active and active self-touch modulates the sense of ownership in a patient with prominent disorders in the body ownership. Moreover, the affect towards the limb became more positive during stroking. Although several limitations restrict the implications of the results, this study provides an indication that self-touch, especially active self-touch helps reinstate the body representation and the sense of ownership. This suggests that self-touch not only plays a role in primary somatosensory deficits, but can modulate impairments in the bodily experience as well. These findings raises new hypothesis for future studies on the role of self-touch on bodily experience.

Acknowledgements

We thank Annette Baars-Elsinga and Anne Visser-Meily for their help with this study.

Chapter 6

Affective touch modulates the rubber hand illusion

H.E. van Stralen
M.J.E. van Zandvoort
S.S. Hoppenbrouwers
L.M.G. Vissers
L.J. Kappelle
and
H.C. Dijkerman

As published as research article in Cognition 2014, 131(1), 147-158.
And as research highlight in Nature 2014, 506, 268

H.E.S, M.J.E.Z, and H.C.D designed research; H.E.S. and L.M.G.V. performed research; H.E.S, S.S.H, and H.C.D. performed; H.E.S., M.J.E.Z., S.S.H., L.J.K, and H.C.D. wrote the paper.

Abstract

Humans experience touch as pleasant when this occurs with a certain velocity (1-10 cms/s). Affective, pleasant touch is thought to be mediated by a distinct neural pathway consisting of un-myelinated tactile afferents (C tactile fibers) that respond to stroking with a slow velocity on the hairy skin. As pleasant touch provides additional information on bodily signals we hypothesized that, compared to regular touch, pleasant touch would have a stronger effect on body ownership as measured through induction of the rubber hand illusion (RHI). Two experiments involving the RHI were conducted. In the first experiment, the effects of stroking velocity (3cm/s and 30cm/s) and stroking material (soft/rough) on the RHI were tested. In the second experiment, the effect of an additional stroking velocity (0.3cm/s) and side of stimulation (hairy and glabrous) was examined. The first experiment showed that slow velocity stroking in combination with a soft material was not only regarded as most pleasant but also resulted in an enhanced RHI on proprioceptive drift and temperature measurements. In the second experiment, we confirmed that stroking with a velocity of 3cm/s resulted in a larger RHI in terms of proprioceptive drift. In addition, compared to regular touch, pleasant touch of the hairy skin resulted in a larger proprioceptive drift, while similar stroking on the glabrous side of the skin did not induce a stronger effect of RHI on proprioceptive drift. Our data suggest that pleasant touch modulates the body representation which is consistently reflected in a larger proprioceptive drift. Our data also suggest that C tactile fibers are likely to be involved in the modulation of body ownership.

Introduction

The sense of touch plays an important role in interpersonal communication and can elicit a strong emotional experience; from a sensual caress to a pat on the hand signaling danger, or a stroke on the head to sooth a child. Touch that is regarded as pleasant facilitates bonding and interpersonal communication, one of foundations of emotions and motivation (Rolls, 2010). Pleasant touch also affects bodily functions such as blood pressure and heart rate (Grewen, Anderson, Girdler, & Light, 2003), hormone secretion (Ditzen et al., 2007) and improves visual-motor skills in low birth weight infants (Weiss, Wilson, & Morrison, 2004). Interestingly, pleasant touch has recently been shown to be processed by an anatomically and functionally distinct system, in parallel to the pathway for discriminative touch (Gordon et al., 2011; McGlone et al., 2007; India Morrison et al., 2010; Olausson et al., 2008). Pleasant touch consists of a light, soft touch to hairy skin with a stroking velocity range of 1-10cm/s (Loken, Wessberg, Morrison, McGlone, & Olausson, 2009; McGlone et al., 2007; India Morrison et al., 2010). The neurological pathways through which pleasant touch is conveyed consists of slow-conducting, unmyelinated low-threshold mechano-receptive fibers (C tactile fibers) that project to the posterior insular cortex (Björnsdotter et al., 2009; India Morrison et al., 2010; Olausson et al., 2002; Olausson, Wessberg, Morrison, McGlone, & Vallbo, 2010). The posterior insula is thought to be involved in the encoding of internal bodily signals to provide information about the current physiological state of the body that are linked to emotional processes (Craig, 2002; Farrell, Laird, & Egan, 2005). Several lines of research also implicate the posterior insula in the experience of body ownership (Baier & Karnath, 2008; Craig, 2002, 2009; Tsakiris, Hesse, Boy, Haggard, & Fink, 2007a), although other evidence suggests that regions (strongly connected to the insula) such as the ventral premotor cortex and areas involved in multisensory integration such as the intraparietal sulcus (Berti et al., 2005; Ehrsson, 2005; Ehrsson, Spence, & Passingham, 2004; Ehrsson, Wiech, Weiskopf, Dolan, & Passingham, 2007; Guterstam, Gentile, & Ehrsson, 2013; Makin, Holmes, & Ehrsson, 2008). These regions are involved in the integration of visual, tactile and proprioceptive information, which is thought to be the foundation for creating a sense of ownership over a limb (Ehrsson et al., 2004; Graziano, 1999; Lloyd, Shore, Spence, & Calvert, 2003).

A widely used paradigm to investigate body ownership is the Rubber Hand illusion (RHI) (Matthew Botvinick & Cohen, 1998). In this illusion, a visible rubber hand and the covered hand of the participant are stroked congruently and synchronously (Matthew Botvinick & Cohen, 1998), after which participants experience the touch applied to the rubber hand as if it was applied to the own hand, suggesting that the rubber hand has now been incorporated in the representation of their own body. A crucial component of the RHI is that manipulations of multisensory input (vision, touch, proprioception) cause profound changes in higher-order body representations (Holmes, Calvert, & Spence, 2007; Tsakiris & Haggard, 2005). Recent studies also suggest a link between the RHI and emotion. A higher ability to recognize emotional states predicts the magnitude of the RHI (Germine, Benson, Cohen, & Hooker, 2013) and threatening a rubber hand causes an anxiety response (Ehrsson et al., 2007). These findings suggest a connection between emotional states and the RHI. However, the influence of affective tactile input on the rubber hand illusion has received limited attention. This is unexpected, since pleasant touch adds information to bodily signals and it might therefore be used form a representation of the body. A study of Schutz-Bosbach et al. (Schutz-Bosbach, Tausche, & Weiss, 2009) examined the effect of pleasantness of stroking material on the RHI, but not stroking velocity, and did not find differences. A recent study of Crucianelly (Crucianelli et al., 2013) found an effect of stroking velocity on the subjective experience of the RHI. Unfortunately, this study failed to explicate which aspect of the stimulation resulted in an enhanced RHI, since factors such as site of stimulation and the duration of visuotactile congruent information was not taken into account. In the current study, the effects of pleasant touch on the body representation as quantified through the RHI were examined. In the first experiment, the effects of pleasant vis-à-vis regular touch were explored. The tactile input was manipulated by changing the stroking velocity as well as the stroking material. In a second experiment, the effects of stroking velocity and potential involvement of C tactile fibers were further scrutinized by comparing pleasant touch to stimulation with an additional velocity and at a part of the arm not containing c tactile fibers (i.e., glabrous skin). Due to additional involvement of C tactile fibers in pleasant touch, we anticipated that pleasant touch would have a stronger effect on the RHI than regular touch.

Experiment 1

Methods

Subjects

Twenty-one healthy volunteers participated in the study (10 male), age range 17-33 years. For all outcome measures, one participant was excluded (>3SD above the mean). The subjects received financial compensation for their participation. Handedness was assessed using the 'Van Strien Dutch Handedness Questionnaire' (Van Strien, 1992). The sample consisted of 13 right-handed, 5 left-handed, and 2 ambidextrous participants. The experiment was performed in accordance with the declaration of Helsinki, and the protocol was deemed to be without psychological or medical risks, and complied with good ethical standards by the ethical advisory committee of the Faculty of Social and Behavioral Sciences at Utrecht University.

Material

Stroking

Stimulation was delivered with two different stroking materials, one optimal for pleasant touch (Clinique goat's hair foundation brush, width 2.6×2 cm, pressure approximately 11.5Pa) for pleasant touch and one not specifically aimed to induce a pleasant experience (plastic rough texture, mesh 7, width 2.6×0.5cm/s, pressure approximately 8.3Pa).

The RHI was induced using two different stroking velocities, about 3.0cm/s optimal for pleasant touch and about 30cm/s suboptimal for pleasant touch. The length of the strokes was 15 cm with an irregular interval varying from 2 to 3 seconds. For the 3cm/s, 12 strokes were applied each trial, whereas 30 strokes were applied for the 30cm/s. The length of the strokes was measured by a ruler that was attached to the inner wall of the wooden framework (not visible for the participant). The number of strokes was counted and randomly checked by a second experimenter. In total the duration of material-skin contact was 60 seconds for the slow velocity stroking an 15 seconds for the high velocity stroking. This procedure was practiced and video-recorded in advance to verify stroking velocity.

Set-up

The experimental set-up of inducing the RHI was adopted from the study by Kammers et al. (Kammers, de Vignemont, et al., 2009). In short, participants were seated behind a desk with a wooden framework (75 cm × 50 cm × 25 cm) containing a movable board that can be placed either vertically (occluding only the right hand during tactile stimulation) or horizontally (occluding both hands of the participant and the rubber hand during registration of perceived hand locations). Subjects were asked to place their forearms in fixed positions (49 cm between index fingers) in the framework with palms down, such that hairy skin (containing C tactile fibers) of both forearms and hands was facing upwards. The rubber hand (including a forearm) was placed 14 cm to the left of the participant's right hand (again measured between index fingers) in an anatomically congruent position. See Figure 1. The proximal end of the rubber hand was occluded by the framework. Stroking stimulation was administered either synchronously (i.e. tactile stimulation to the invisible subject's hand and corresponding visual stimulation to the visible rubber hand are applied simultaneously) or asynchronously (i.e. there is a temporal discrepancy between the tactile stimulation of the rubber hand and the subject's hand).

Procedure

Table 1 | The experimental within subject design of experiment 1. All eight conditions were conducted twice per participant, sixteen trials per participant in total.

	Experimental Condition			
	Synchronous stroking		Asynchronous stroking	
Stroking Velocity (cm/s)	Soft brush	Plastic mesh	Soft brush	Plastic mesh
3	1.	3.	5.	7.
30	2.	4.	6.	8.

The participant (not the experimenter) was blind to the purpose of the experiment. The subjects were seated comfortably behind a desk with the experimental framework and were asked to place their arms in the position as described above. Before each stimulation period, skin temperature and perceived location of both hands was obtained. Stroking was applied on the dorsal surface of the hand in a proximal to distal direction with an unpredictable starting point for 90 seconds. After this stimulation period, the participants were instructed to close their eyes so that the movable board could be placed horizontally on the framework to occlude the own hands and the rubber hand from vision. At that point in time, skin temperature was measured again, and participants were asked to open their eyes and verbally report when the experimenter's index finger resembled (mirrored) the perceived location of their own index fingers. Participants were requested to complete the 'Rubber Hand Illusion Questionnaire' (Matthew Botvinick & Cohen, 1998; Kammers, de Vignemont, et al., 2009) and given the opportunity to move and look at their own hands. The procedure of stimulation, temperature measurements, estimation of hand location and questionnaires was repeated until each condition (eight trial types, see Table 1) was measured twice, so sixteen trials in total per participant. Latin square balancing was applied. After the experiment was completed, participants were asked to rate pleasantness of the four different combinations of stroking velocity and material.

Outcome measures

Participants rated the pleasantness of the four stroking conditions (low velocity- soft brush, high velocity- soft brush, low velocity- plastic mesh and high velocity- plastic mesh) on a five point Likert-rating scale after completed the entire experiment. The effect of the RHI was quantified with the following three measures: 1) proprioceptive drift (Pd) (Matthew Botvinick & Cohen, 1998), 2) temperature difference (Td) (Moseley et al., 2008) and 3) a questionnaire to test the subjective experience of the strength of the illusion (Matthew Botvinick & Cohen, 1998; Kammers, de Vignemont, et al., 2009). The questionnaire consists of ten statements

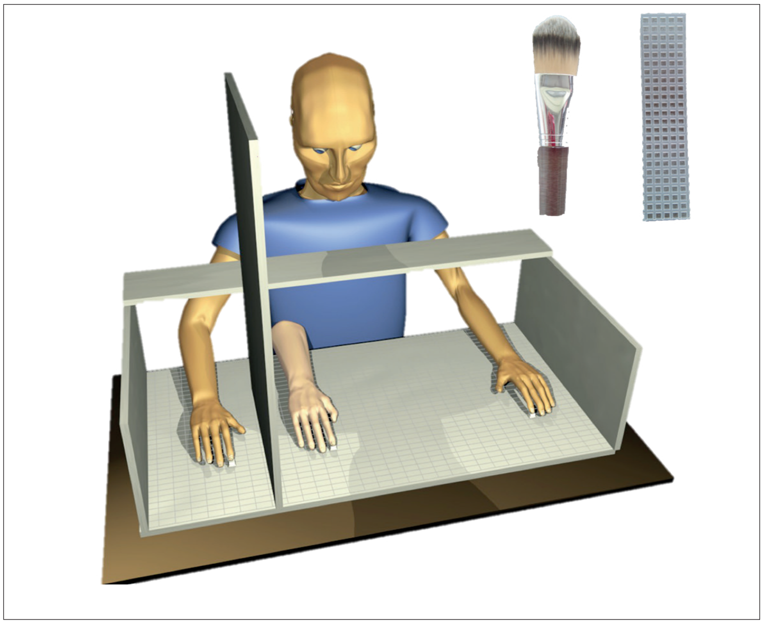

Figure 1 | The experimental within subject design of experiment 1. The participant was stroked with either a soft brush or a plastic mesh on the dorsal (hairy) side of the arm.

Table 2 | The Rubber Hand Illusion questionnaire. Participants were asked to indicate the degree of agreeability on a Likert-scale (1-10).

Instructions: Please keep the last trial in mind when rating the following questions according to a 1-10 scale ('1' means 'I strongly disagree', '5' means 'neutral', and '10' means 'I strongly agree'). During the last trial there were times when:

1.	It seemed as if I was feeling the touch at the location where I saw the rubber hand being touched.
2.	It seemed as though the touch I felt was caused by the stimulation on the rubber hand.
3.	I felt as if the rubber hand was my own hand.
4.	It felt as if my real hand was drifting toward the rubber hand.
5.	It felt as if I had more than two hands or arms.
6.	It seemed as if the touch I was feeling came from somewhere between my own hand and the rubber hand.
7.	It felt as if my real hand was turning 'rubbery'.
8.	It appeared (visually) as if the rubber hand was drifting toward my own hand.
9.	The rubber hand began to resemble my own (real) hand, in terms of shape, skin tone, freckles or some other visual feature.
10.	It felt as if the rubber hand and my own dominant hand lay closer to each other.

6

that required a rating of the strength of (dis)agreement. The first three statements are illusion-related and the remaining seven items serve as control statements (see Table 2). To assess proprioceptive drift (Pd) a ruler was attached to the wooden framework (not visible to the participant) and the experimenter moved her index finger from the midline to the edges of the framework, or vice versa, with starting positions counterbalanced. The participants verbally report when the experimenter's index finger resembled (mirrored) the perceived location of their own index finger. Deviations between actual position and pe rceptual position of the hand were obtained. The Pd was calculated by subtracting the deviation score (between actual and perceived position of the hand) after asynchronous stroking from the deviation score after synchronous stroking. Thus, Pd=(judgment of finger location before synchronous stroking minus judgment of finger location after synchronous stroking) minus (judgment of finger location before asynchronous stroking minus judgment of finger location after asynchronous stroking). Temperature measurement was conducted with a Raytek handheld Autopro (ST25) laser thermometer. The lasers were pointed on the proximal phalanx of the hands before and after stimulation and on both hands and the difference between those measurements were calculated. The non-stimulated hand was also measured before and after stimulation and served as a control. The temperature difference (Td) is calculated by the subtracting the temperature after stroking from the temperature before stroking in the synchronous condition corrected for the temperature difference in the asynchronous condition, thus Td=(T after asynchronous stroking minus T before asynchronous stroking) minus (T after synchronous stroking minus T before synchronous stroking).

Analyses

The design consists of a 2×2 within subject design (two levels of material and velocity). To verify whether the stroking with a slow velocity and a soft brush were indeed rated as more pleasant than stroking with a high velocity and/or plastic mesh, Friedman's ANOVA and Wilcoxon signed ranks tests were performed using SPSS 19.0 on the mean Likert-scale ratings. For the subjective illusion strength (questionnaire), the proprioceptive drift and the temperature drop, the difference scores between the synchronous and asynchronous conditions was calculated, and the repeated measure ANOVA was applied on two factors with two levels (material and velocity). This way, the data was corrected for effects as a result of stroking in general and isolate the effects of the illusion only.

Results experiment 1

Pleasantness ratings

Pleasantness of the stroking appeared to be significantly different between the four stroking conditions $X^2(3)=45.7$, $p<.001$. (See figure 2) Stroking with a velocity of 3cm/s was rated as more pleasant than a stroking velocity of 30cm/s independent of the material that was used (soft material $T=136$, $r=.6$ $p<.01$, rough material $T=85.5$, $r=.46$ $p<.01$). In addition, stroking with soft material was rated as more pleasant than stroking with rough material, independent of stroking velocity (low velocity $T=171$, $r=.60$ $p<.01$, high velocity $T=136$, $r=.56$, $p<.01$). There was no significant interaction effect between stroking velocity and stroking material.

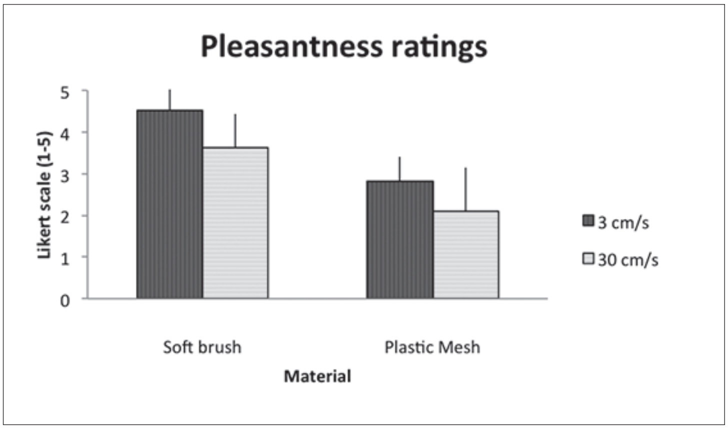

Figure 2 | Pleasantness ratings of the different stroking conditions. A main effect of stroking velocity and stroking material was found to be significant.

Subjective illusion strength

Subjects completed a questionnaire after each stimulation period to assess the subjective illusion strength. The mean ratings for all statements are shown in Figure 3a. Results showed that for the ten statements, participants only rated statements 1, 2 and 3 (the illusion-related) and statement 9 (control statement) above 5 (above neutral) after synchronous stimulation, but not after the control conditions (asynchronous stimulation). The results of these statements are displayed in Figure 3b. A more in-depth analysis of the effect on the illusion (synchronous stroking ratings corrected for asynchronous stroking) was conducted on the illusion-related statements to assess whether the different stroking conditions had a distinct influence on the subjective experience of the illusion. For the first statement- it seemed as if I was feeling the touch at the location where I saw the rubber hand being touched- there was a significant main effect of stroking velocity $F(1,19)=9.10$, $p<.01$. There was neither a main effect of material nor an interaction effect of stroking velocity and material. For the second statement- it seemed as though the touch I felt was caused by the stimulation on the rubber hand- there was no significant main effect of stroking velocity, stroking material, nor an interaction effect between those factors. For the third statement -I felt as if the rubber hand was my own hand- there was no significant main effect of stroking velocity, stroking material, nor an interaction effect between those factors. For statement 9 - The rubber hand began to resemble my own (real) hand, in terms of shape, skin tone, freckles or some other visual feature- there was no significant main effect of stroking velocity, stroking material, nor an interaction effect between those factors.

In sum, for all illusion-related statements, participants experience a higher rubber hand illusion after synchronous stimulation compared to asynchronous stimulation. Difference-scores between synchronous and asynchronous stroking revealed an effect of stroking velocity on statement 1, and not on the other statements.

Proprioceptive drift (Pd)

For the non-stimulated hand, no Pd was found as a result of stroking the right hand. For the stimulated hand a main effect for material was found $F(1,20)=4.94$ $p<.05$, with mean difference of .84 cm SE .37 with a higher Pd when a soft brush was used instead of a plastic mesh, $t(19)=2.22$ $p<.05$. Moreover, a main effect for velocity was found $F(1,20)=12.4$ $p<.01$ with a mean difference of .79 cm SE .27 with a higher Pd after stroking with a low velocity compared to a high velocity, $t(19)=2.89$ $p<.001$. Finally, an interaction effect was found between material and velocity $F(1,20)=14.88$ $p<.01$, with a higher difference between the two stroking velocities for the soft brush compared to the plastic mesh $t(19)=3,77$ $p<.001$ see Figure 4a.

Temperature difference (Td)

For the non-stimulated hand, no effect of stroking velocity or material was found on the temperature of the hand. For the stimulated hand, a factorial repeated measure ANOVA revealed a significant main effect for material $F(1,20)=9.84$ $p<.01$ with a higher drop in temperature after soft brush stimulation compared to the use of a plastic mesh, $t(19)=-3.14$ $p<.001$ with a mean difference of $-.42^{0}$C SE .13, Moreover, the stroking velocity influenced the temperature on a significant level as well $F(1,20)=5.93$ $p<.05$ with a higher temperature drop for stroking with a low velocity, $t(19)=-3.14$ $p<.001$ with a mean difference $-.45^{0}$C SE .19. There was a trend towards an interaction effect between material and velocity, although this was not significant $F(1,20)=4.01$ $p=.059$. See Figure 4b.

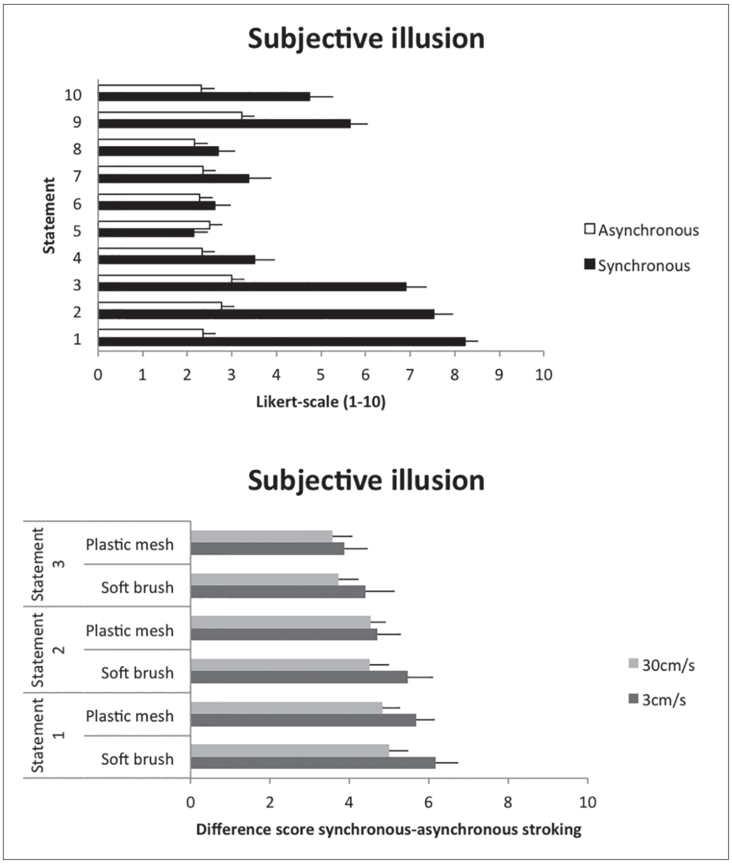

Figure 3 | Subjective Illusion strength. a): Ratings (1-10) on the RHI questionnaire for all statement for the synchronous and asynchronous condition. The statements 1, 2 and 3 (illusion related statements) and statement 9 (control statement) are rated above neutral (score 5) and significantly different between synchronous stroking and asynchronous stroking b): Difference scores between synchronous and asynchronous stroking for the two stroking velocities and two stroking material for the three illusion-related statements.

To summarize the results, 3cm/s stroking was regarded as more pleasant compared to 30cm/s and soft material stroking was rated as more pleasant compared to rough material. For the RHI outcome measures, 3cm/s stroking affected only statement 1 of the questionnaire. For the proprioceptive drift, an effect of stroking velocity as well as material was found. A comparable pattern was found for temperature difference as a result of the stroking, i.e. a larger drop in temperature after slow velocity stroking with a soft brush compared to the control conditions, suggesting an objective stronger illusion.

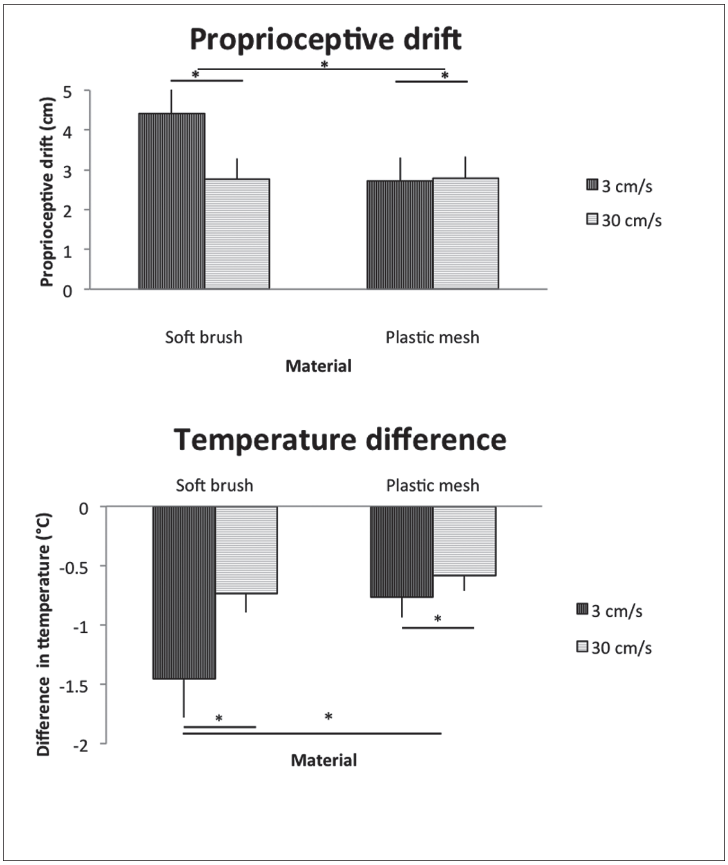

Figure 4a | The proprioceptive drift (Pd). The graph shows that low velocity stroking resulted in a significant higher Pd compared to high velocity stroking. In addition, stroking with a soft brush resulted in a significant higher Pd compared to stroking with a plastic mesh. The interaction effect between velocity and material appeared to be significant as well. Error bars represent standard deviation. Asterix represent significant differences (p<.05). **Figure 4b | The temperature difference (Td)**. The graph shows that low velocity stroking resulted in a significant larger Td compared to high velocity stroking. In addition, stroking with a soft brush resulted in a significant larger Td compared to stroking with a plastic mesh. Error bars represent standard deviation. Asterix represent significant differences (p<.05)

Discussion Experiment 1

The first experiment investigated the influence of pleasant touch on body representation as quantified through induction of the rubber hand illusion. By altering tactile stimulation, we found that pleasant touch, (i.e. stroking with a low velocity and soft material) induced a stronger rubber hand illusion than faster and rougher touch. The strength of the influence of pleasant touch on the rubber hand illusion was reflected by the finding that a larger effect was present in two out of three outcome measures. That is, the objective indices of the RHI (proprioceptive drift and temperature drop showed that the body representation was more strongly influenced by pleasant touch than by touch that was less pleasant. This was not the case for the subjective measure (the questionnaire) for which only an effect of velocity was found on one of the illusion related questions.

Two factors may obscure clear interpretation of these results. First, the conditions with different stroking velocities differ in terms of exposure to congruent visuo-tactile stimulation. That is, during the 3cm/s condition, the duration that visual and tactile input is congruent is larger. Therefore, to control for differences in visuo-tactile stimulation a third slower velocity (0.3cm/s) was incorporated in the follow-up experiment, which involves longer stroking time, but does not activate the C tactile fibers (experiment 2a). Second, to elucidate the distinct contribution of C tactile fibers to the RHI, a control condition involving stimulation of the palm of the hand was added (experiment 2b). As C tactile fibers are only present in hairy skin, pleasant stimulation of glabrous skin should not induce a stronger RHI. The second experiment was conducted with the soft brush only.

For experiment 2a, following the study of Loken et al. (Loken et al., 2009) an inverted U shape curve with an optimal response for the 3cm/s stroking condition was expected. For experiment 2b, it was anticipated that tactile stimulation of the glabrous skin would not induce a stronger RHI. Specifically, we expect a smaller illusion between the two stroking velocities when the illusion was administered on the ventral side of the hand compared to the dorsal side of the hand. We also expect to replicate the findings of the first experiment (soft brush, 3 and 30cm/s), i.e. an enhancement of Pd, Td and statement 1 of the questionnaire for the 3cm/s compared to the 30cm/s stroking condition.

Experiment 2

Methods

Subjects

Twenty-eight healthy volunteers participated in the study, 14 males, mean age 32 (±12.2). The subjects received financial compensation for their participation. Handedness was assessed using the 'Van Strien Dutch Handedness Questionnaire' (Van Strien, 1992). The sample consisted of 26 right-handed participants. Outliers (>3SD from the mean) were excluded per outcome measure for analyses, i.e. four participants for the proprioceptive drift and temperature difference, three participants for the pleasantness ratings and one participants was excluded before analyzing the subjective experience of the illusion.

Table 3 | The experimental within subject design of experiment 2a and 2b. All ten conditions were conducted twice per participant, twenty trials per participant in total.

Stroking velocity (cm/s)		Dorsal		Ventral	
		Synchronous	Asynchronous	Synchronous	Asynchronous
		Experiment 2a			
0.3		1	2		
3	Experiment 2b	3	4	7	8
30		5	6	9	10

Material and set-up

The RHI was induced using three different stroking different stroking velocities, about 0.3cm/s, 3.0cm/s and 30cm/s and two different sides of stimulation, i.e. dorsal and ventral side. To provide a constant stroking velocity, a ruler on the inside of RHI set-up indicated the distance of 15 cm a stopwatch verified the duration of each strokes (respectively 50 seconds, 5 seconds an 0.5 second). The number of strokes was counted and randomly checked by a second experimenter. In total the duration of material-skin contact was 88 seconds for the 0.3cm/s stroking velocity, 60 seconds for the 3cm/s condition and 15 seconds for the 30cm/s stroking condition. This procedure was practiced in advance and video-recorded to verify stroking velocity. Stimulation was delivered only with the soft material used in the first experiment. The experimental set-up was similar as in the first experiment. For the stimulation on the dorsal side of the hand, the position between the index finger of rubber hand and the index finger of the own hand remained 14 cm. For the simulation on the ventral side, both the own arms of the participants as the rubber arm were placed in the framework in fixed position, palms up. The position of middle fingers in the ventral stimulation conditions matched the position of the middle fingers in the dorsal stimulation. In this way, the position of the hands remained as constant as possible, but the position of the index finger was shifted slightly more to the body midline in the ventral stimulation condition (see Figure 5). The distance between the index fingers in the ventral stimulation was 14 cm. Stroking stimulation was administered either synchronously or asynchronously.

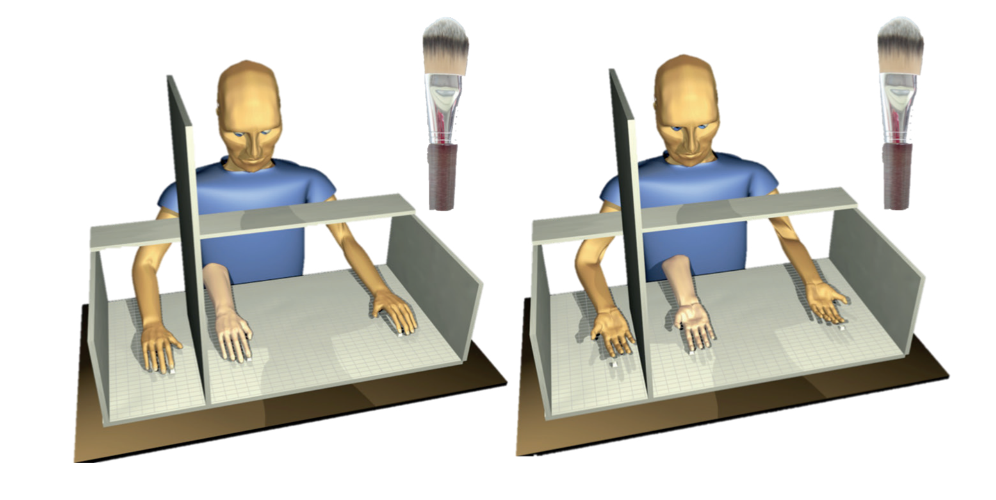

Figure 5 | Experimental set-up of experiment 2b. The rubber hand and the own hand was stimulated on the dorsal (hairy) and ventral (glabrous) side of the hand. Stimulation was conducted with a soft brush.

Procedure and outcome measures

The procedure was similar to the procedure in experiment 1 only with different stroking conditions (see Table 3). In total, 20 trials were conducted, each condition was measured twice. For the subjective illusion, the RHI questionnaire was obtained after each trial. The proprioceptive localisation of the index finger was measured after each trial for both hands. The temperature of the hand was measured before and after each trial on both hands. For the ventral stimulation conditions, temperature was measured on the palm of the hand. For the subjective illusion experience, a visual analogue scale was added to the Rubber Hand Illusion questionnaire, to indicate the pleasantness of the stroking after each trial.

Analyses

For experiment 2a, an ANOVA repeated measure was conducted for the pleasantness ratings, the subjective experience of the illusion, the proprioceptive drift and the temperature with one factor (stroking velocity) and three levels (0.3cm/s, 3cm/s and 30cm/s). The slowest and highest stroking velocity were compared with the 3cm/s stroking by simple planned contrast. As in the first experiment, the values of all three outcome measures were calculated by subtracting the values of the asynchronous from the synchronous stroking conditions. For experiment 2b, an ANOVA repeated measure was conducted on all outcome measures with two factors, stroking velocity (3cm/s and 30cm/s stroking) and side of stimulation (hairy and glabrous).

Results Experiment 2a

Pleasantness ratings

A main effect of the pleasantness ratings for the three stroking condition was trending towards the significant level, $F(46, 2)=3.1$, $p=.055$. Planned contrasts revealed that the 3cm/s stroking was rated significantly higher compared to stroking with a slower $F(1,23)=5.66$ $p<.05$ and higher velocity $F(1,23)=4.56$ $p<.05$. See Figure 6.

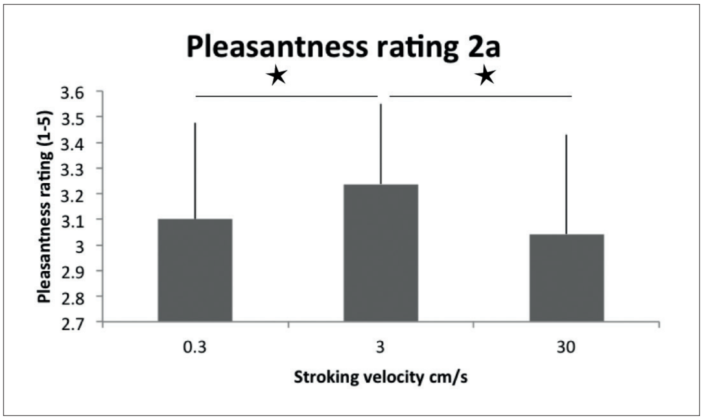

Figure 6 | Pleasantness rating of the three different stroking velocities. The 3cm/s stroking velocity was judged to be significantly more pleasant compared to the other velocities.

Subjective illusion strength

Results show that for the ten statements, participants only rated the statement 1, 2 and 3 (the illusion related statements) above neutral after synchronous stimulation, but not for the control conditions (asynchronous stroking). As in experiment 1, the difference scores between synchronous and asynchronous stroking was calculated. Regarding statement 1, there was a significant main effect stroking velocity $F(2,52)=3.44$ $p<.05$. Planned contrasts revealed a significant higher rating for the 3cm/s compared to the 0.3cm/s stroking condition $F(1,26)=5.29$ $p<.05$, but no difference between the 3cm/s and 30cm/s stroking was present. For statement 2, there was a significant main effect stroking velocity $(2,52)=4.63$ $p<.05$. Again, planned contrasts showed no significant differences between the 3cm/s and the other stroking velocities, although there was a trend towards a difference with the 0.3cm/s stroking $F(1,26)=3.78$ $p=.063$. For statement 3, there was a no main effect of stroking velocity.

Proprioceptive drift (Pd)

For the non-stimulated hand, no effect on Pd was found as a result of inducing the RHI on the other hand. For the stimulated hand, a main effect of velocity was found $F(2,46)=4.71$ $p<.05$. Pairwise comparisons showed a significant difference between the 3cm/s and the 0.3cm/s $t(23)=2.42$ $p<.05$ and between 3cm/s and 30cm/s $t(23)=2.43$ $p<.05$. The slowest and highest velocity did not differ from each other. See Figure 7.

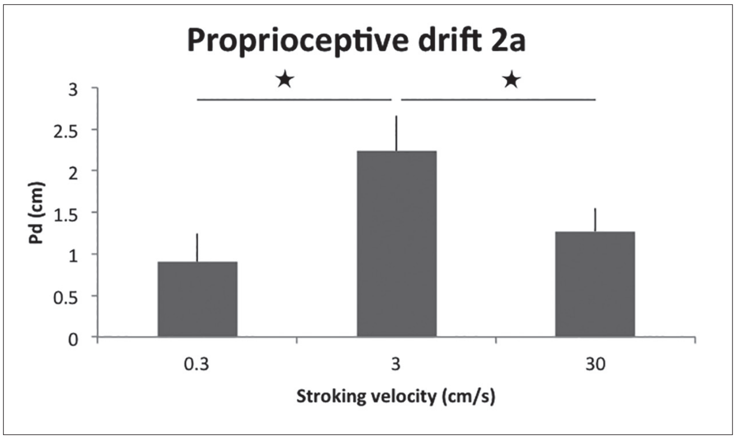

Figure 7 | The proprioceptive drift of experiment 2a. The 3cm/s stroking condition was significantly higher compared to the slowest (0.3cm/s) and highest stroking velocity (30cm/s).

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Temperature difference (Td)

There was no effect of temperature found between the different conditions, i.e. no main effect of experimental condition, velocity or the interaction between these factors reached the level of significance.

Summary Experiment 2a

In this experiment the effect of stroking velocity on the RHI was examined. First, the 3cm/s stroking was indeed rated as being more pleasant than the faster or slower velocities. With respect to the RHI, a stroking velocity of 3cm/s induced a stronger RHI when compared to 0.3cm/s and 30cm/s for Pd. Importantly, 0.3cm/s and 30cm/s did not differ in terms of Pd. This finding suggests that longer visuotactile stimulation does not induce a stronger RHI and therefore corroborates the hypothesis that pleasant touch has stronger effect on the RHI, perhaps due to unique involvement of C afferent fibers. For the subjective illusion of the RHI, we found a stroking velocity effect for statement 1 and 2, and not for statement 3. The effects on statement 1 and 2 were driven by the decreased subjective illusion for the 0.3cm/s stroking velocity as opposed to the higher stroking velocities suggesting that the effect of speed as found in the first experiment (statement 2) is not specific for the 3cm/s condition. It can be argued that a rating of a particular condition is influenced by the other conditions in the experiment. That is, the subjective illusion reflects the relative judgment of the stroking condition rather than an absolute measure of the particular condition. For Td, we could not replicate the findings of the first experiment, nor did we find a change in hand temperature as a result of stroking velocity.

Results Experiment 2b

Pleasantness ratings

A significant interaction effect between velocity and stimulation side was found on the pleasantness ratings $F(1,24)=11.10$, $p<.01$. See figure 8. Specifically, the pleasantness ratings for dorsal side stimulation differed between the 3cm/s and 30cm/s stroking velocity $F(1,23)=4.56$ $p<.05$ and this difference was not significant with ventral side stimulation.

Subjective illusion strength

For the dorsal as well as the ventral stimulation, participants rated the illusion related statements above neutral after synchronous stroking, but not after asynchronous stroking, suggesting that for both sides of stimulation the rubber hand illusion was successfully conducted. Analysing the difference scores between synchronous and asynchronous stroking, we found no effect of stroking velocity or side of stimulation (hairy of glabrous skin) on any of the illusion related statements (1, 2 and 3).

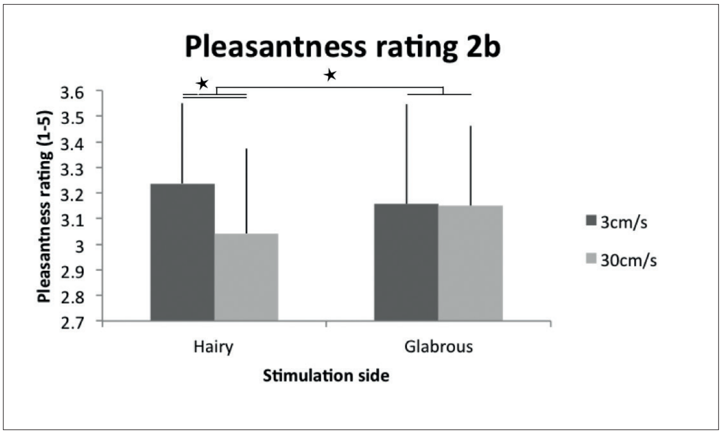

Figure 8 | Pleasantness rating experiment 2b. Participants rated a stroking velocity of 3cm/s as more pleasant as opposed to 30cm/s on hairy, and not glabrous skin.

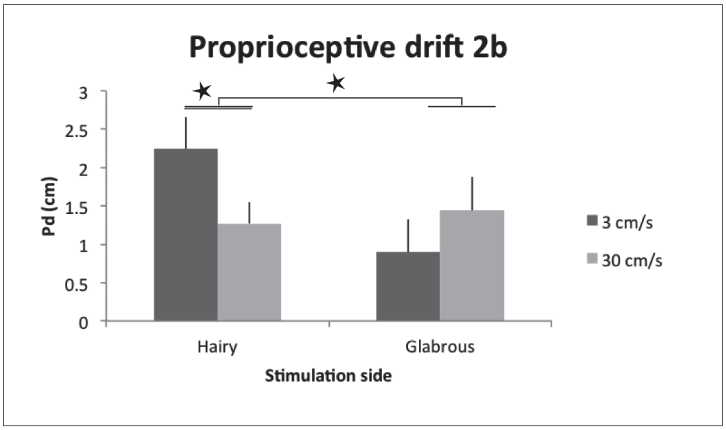

Figure 9 | Proprioceptive drift of experiment 2b. Participants showed a higher proprioceptive drift after RHI for slow velocity stroking compared to high velocity stroking on hairy, and not glabrous skin.

Proprioceptive drift (Pd)

No effect on Pd was found as a result of the RHI for the non-stimulated hand. For the stimulated hand, an interaction effect of side of stimulation x velocity was observed $F(1,23)=4.61$ $p<.05$. See figure 9. Pairwise comparisons showed a significant difference between the 3 and 30cm/s stroking condition on the dorsal side $t(23)=2.43$, $p<.05$ with a higher mean Pd for the 3cm/s (2.24 cm SE .41) compared to the 30cm/s (1.27cm SE .28). For ventral side stimulation, the difference between the 3cm/s velocity (.90 cm SE .42) and 30cm/s (1.43 cm SE .44) was not significant.

Temperature difference (Td)

No effect of stroking velocity nor of side of stimulation was found for skin temperature.

Summary Experiment 2b

In this experiment, involvement of C tactile fibers was explored through stimulation (3cm/s and 30cm/s) of the hairy versus glabrous skin. For Pd, the results reconfirmed a higher proprioceptive drift for the 3cm/s stroking, compared to the 30cm/s stroking on the hairy skin. As C tactile fibers are not present in glabrous skin, the observed absence of a Pd-difference between pleasant (3cm/s) and regular touch (30cm/s) of the glabrous skin, suggests involvement of C tactile fibers. In contrast, although the pleasantness of 'pleasant' stroking (3cm/s) of hairy skin was rated higher than for 'pleasant' stroking of the glabrous skin (Loken et al., 2009; McGlone et al., 2007), 3cm/s stroking induced a similar subjective illusion (as measured with the questionnaire) after stimulation of the hairy and glabrous skin. Regarding the temperature drop, we did not find differences in stroking velocity, neither in side of stimulation. This result did not replicate our findings of our first experiment or findings of previous studies (Hohwy & Paton, 2010a; Moseley et al., 2008) demonstrating that this measure is a less robust outcome measure of the RHI. One important factor that could have influenced the temperature changes is the difference in room temperature between the two experiments; the temperature of the room in the second experiment was significantly higher (performed during the summer) than in the first (performed during the winter). The difference between room and hand temperature was therefore much smaller in the second experiment, potentially refraining the hand from cooling down as much.

General discussion

In the current study we examined the influence of pleasant touch on body ownership as measured through induction of the RHI. Results show that pleasant touch has a stronger influence on the RHI than regular touch. That is, the proprioceptive drift (Pd) was larger when the RHI was conducted with a soft material compared to rough material. Furthermore, the enhanced Pd was specific to the 3cm/s stroking and not slower or higher stroking velocities. This effect was found only for stimulation on the hairy skin, but not on the glabrous skin. Stroking with a soft material, at 3cm/s on the hairy skin was regarded as most pleasant, in line with previous studies. The enhanced RHI was consistently reflected in the Pd and not in the subjective experience of the illusion nor was there a reliably higher drop in hand temperature following the pleasant touch.

Our data show that pleasant touch has a stronger effect on the RHI than regular touch and that Pd is a reliable and sensitive index to measure this effect. We propose that the larger RHI is associated with stimulating an additional tactile afferent channel in combination with increased emotional saliency of somatosensory information. In the first experiment, results show a stronger RHI for 3cm/s as opposed to 30cm/s stroking velocity. This is consistent with a recent report showing a larger subjective experience of the RHI for slower compared to faster stroking (Crucianelli et al., 2013). These results, however, are potentially confounded by differences in the magnitude of congruent visuo-tactile stimulation (i.e., the total time during which the brush is in contact with the hand). Since the results from experiment 2a showed that the slowest stroking speed (0.3cm/s) did not differ from the fastest (30cm/s) in terms of Pd, we are able exclude the possibility that increased visuo-tactile congruent information accounts for the enhanced RHI. In addition, results of experiment 2b suggest that pleasant touch of the glabrous skin (i.e., palm of the hand) does not induce a larger illusion when compared with regular touch (30cm/s). This suggests that the number of strokes and the total time during which the brush is in contact with the hand do not explain the increased RHI. Taken together, these findings clearly show that differences in visuo-tactile congruent information are not likely to explain the effects of the enhancement in the RHI.

The increased effect of pleasant touch on the RHI may instead be a consequence of stimulating an additional tactile sensory channel. The RHI allows manipulation of the body representation through synchronized multisensory input. In the current study, multisensory input was changed by activating the C tactile fibers in addition to Aβ fibers that convey discriminative (regular) touch. Therefore, C tactile fibers projecting to the insula (Loken et al., 2009; McGlone et al., 2007; Olausson et al., 2010) may constitute a neurophysiological mechanism through which the additional influence of pleasant touch on the RHI emerges. We propose that this influence is twofold. First, the 3cm/s stroking velocity activates more afferent channels (e.g. C tactile and Aβ fibers) thereby augmenting afferent input which could subsequently lead to a boost of multisensory integration, overruling the proprioceptive localization. Second, the affective experience of the pleasant stroking may result in emotional tagging of synchronized visuotactile input, thereby increasing multisensory integration. The insula is of paramount importance for the encoding of affective components of somatosensory input (Bufalari and Ionta, 2013) and it modulates other brain areas (e.g., S1, S2) involved in processing of affective somatosensation (Macaluso & Driver, 2005). Suboptimal functioning of C tactile fibers projecting to the insula affect the rating of the pleasantness of interpersonal touch but also fail to activate the insula (I Morrison, Loken, & Olausson, 2010). As the insula is implicated in emotional salience monitoring (Taylor et al., 2009) and in the differentiation of the stimulation source, particularly in the light of affective experiences (Ebisch et al., 2011), the additional effect of pleasant touch on the RHI may be mediated by the insula. It is however important to note that other areas, such as the putamen, claustrum, and the secondary somatosensory cortex in the parietal operculum are also highly important in the processing of bodily signals. In addition, fronto-parietal multisensory areas (Makin et al., 2008) are consistently involved in ownership feelings in the RHI paradigm in healthy individuals. It should therefore be stressed that signals from affective touch, possibly processed in the insular cortex (Olausson et al., 2010), may be further processed and integrated with visual, proprioceptive, and other sensory signals at the level of the multisensory fronto-parietal cortex.

The finding that pleasant touch influences body representation is substantial and provides a connection between different processes involved in emotional labeling of somatosensation on the one hand, and body ownership on the other hand. Numerous studies have shown an effect of touch on bodily functions and bodily development (Gallace & Spence, 2010). For example, being caressed by a spouse can reduce heart rate, blood pressure and hormone secretion and touch given to low birth weight infants improves visual-motor skills (Weiss et al., 2004). Furthermore, tactile input help newborns generate a representation of their bodily self which occurs already at 7 months old (Cowie, Makin, & Bremner, 2013). Our results suggest that a pleasant component of tactile stimulation modulates the body representation beyond that of regular tactile stimulation.

The effect of pleasant touch on the body representation may also have clinical implications. Currently, treatment of body representation disorders has received limited attention, although this is a common side effect of non-congenital brain trauma. Recently we reported a stroke patient who denied ownership over her arm after an ischemic stroke (somatoparaphrenia) and who showed remarkable effects of caressing her arm (van Stralen et al., 2011). Pleasant touch may therefore be used as a therapeutic method in patients with problems in body representation (e.g. somatoparaphrenia, body integrity identity disorder). Further studies should assess how modulations such as affective stroking could result in longer lasting effects on body ownership. Similarly, pleasant touch may be used to achieve a sense of heightened ownership over prosthetic body parts in amputees (Ehrsson et al., 2008).

The current study has a few limitations that should be considered. First, our results show a consistent effect of pleasant touch on an objective outcome measure of the RHI (Pd), but not on the subjective experience of the illusion. This could be taken to suggest that C tactile fibers affect the body representation in terms of multisensory integration and hand localization, but are not involved in the conscious experience of body ownership. Also, it supports and extends previous findings suggesting that proprioceptive drift and a subjective experience of hand ownership are two dissociable measures of the RHI (Holmes, Snijders, & Spence, 2006; Kammers, de Vignemont, et al., 2009; Rohde, Di Luca, & Ernst, 2011). Although pleasant touch has a strong and consistent effect on some components of the RHI, it remains unclear why pleasant touch specifically affects the Pd and not the conscious subjective experience of hand ownership. This significant finding does however warrant future research which should explore the underlying mechanisms that make Pd the most consistent and sensitive outcome measure for pleasant touch modulation on body representation. Second, although the current methodological design mainly consisted of the manipulation of bottom-up factors, top down factors may also play a role. For instance, Gazzola and colleagues (Gazzola et al., 2012) found that the pleasantness of an interpersonal situation modulates tactile input and SI activation, independent of the characteristics of cutaneous input. In line, seeing unpleasant pictures can influence somatosensory evoked responses (Montoya & Sitges, 2006) and being touched by a human hand results in a different neural response compared to indirect touch (Kress, Minati, Ferraro, & Critchley, 2011). These studies show that a pleasant experience of sensory input modulates not only the perception but also the primary cortical somatosensory input. Therefore, future studies are advised to also take top-down factors into account.

In conclusion, in the current study we show that the RHI is increased by pleasant touch which may be due to a richer somatosensory input, e.g. activation of an extra tactile channel and/or the affective value of tactile stimulation. Our findings underscore the importance of tactile affectivity for aspects of body representation and may have implications for the development of treatment for body ownership deficits in different patient groups.

Acknowledgments

We would like to thank the reviewers for their critical and insightful comments. We would also like to thank dr. Stefan van der Stigchel for his input, Roderik van Heijst for creating the figures, and Nicole Montijn for assistance in data collection.

Chapter 7

Body representation disorders predict left right orientation impairments after stroke: A Voxel-based lesion symptom mapping study

H.E. van Stralen
H.C. Dijkerman
J.M. Biesbroek
H.J. Kuijf
H. Maarten
A. van Gemert
D. Sluiter
L. J. Kappelle
M.J.E. van Zandvoort

In press: Cortex, 2017

H.E.S., J.M.B., H.C.D., L.J.K., and M.J.E.Z designed research; H.E.S and D.S. performed research; J.M.B and H.J.K. contributed new analytic tools; H.E.S., J.M.B., and H.J.K. analysed data. H.E.S. H.C.D., J.M.B., H.J.K., M.A.G., D.S., L.J.K. and M.J.E.Z wrote the paper

Abstract

Deficits in the ability to distinguish between the left and right side of the body can severely impair daily life functioning. The current study examined the relation between left right orientation (LRO) impairments and somatosensory related deficits, ranging from primary somatosensory impairments to body representation impairments, in patients who suffered a recent stroke. We also examined which areas in the brain are associated with LRO impairments using a Voxel-based Lesion Symptom Mapping (VLSM) analysis. We tested 47 first-ever stroke patients and 48 age-matched healthy controls. LRO was assessed with the Bergen Right Left Discrimination Test (BRLD). Impairments on primary somatosensory function (touch perception, proprioception), higher order somatosensory function (finger gnosis, subjective sense of body ownership) and other cognitive functions (language, attention & working memory, visuospatial neglect) were entered as predictors in a logistic regression analyses. Outcome measures consisted of the BRLD-total performance which was further subdivided in performance for 1) first person perspective stimuli 2) third person perspective stimuli 3) alternating between first- and third person perspective. Impairments on BRLD-total performance was predicted by impairments in finger gnosis and visuospatial neglect. For items placed in third person perspective, performance was predicted by body representation impairments; finger agnosia and the subjective sense of body ownership. VLSM analysis showed a significant association between LRO impairments and damage to the right insula. The current study suggests that the somatosensory system is important for LRO. Furthermore, the results indicate that an affected body representation may hinder adopting a third person perspective that may subsequently also lead to LRO impairments. The right insular cortex appeared crucially involved in these processes.

Introduction

In daily life the ability to distinguish left from right is of profound importance for orientation and navigation. It requires awareness that the left and right side of our body are different and it requires the ability to verbally name the terms 'left' and 'right' (Mendoza & Foundas, 2007). As such, impairments in left right orientation (LRO) can be caused by multiple factors, such as impairments in language, spatial mapping,(Gold, Adair, Jacobs, & Heilman, 1995) and higher order aspects of the somatosensory system, such as body representation deficits (Benton, 1959). Several different body representations have been described (Frederique de Vignemont, 2010; S. Gallagher, 2005; Paillard, 1999), such as action related representations, structural representations and spatial body representations (Head & Holmes, 1911; Schwoebel & Coslett, 2005). A deficit in body representation may result in problems in identifying body parts, such as the fingers in finger agnosia. Indeed, finger agnosia has been related to LRO impairments and is, together with acalculia and agraphia, described as the Gerstmann syndrome which is associated with lesions in the left parietal lobe (Gerstmann, 1940b). Other studies have related LRO to more spatial functions, primarily mediated by the right hemisphere. That is, spatial information is especially important in left- right decisions when mental rotation of the object is required (Ditunno & Mann, 1990; Harris, Harris, & Caine, 2002; Ratcliff, 1979). Mental rotation requires the ability to mentally manipulate (turn, twist or rotate) an image in order to match it to another image (Shepard & Metzler, 1971). In a study of Ratcliff and colleagues (Ratcliff, 1979), brain injured patients performed a LRO task with and without requirement of mental rotation. Results showed that patients with left parietal lesions made more errors than patients with right parietal lesions when the stimuli where presented in a first person perspective whereas this was the other way around if the stimuli had to be mentally rotated. In line with these results, Harris and colleagues (Harris et al., 2002) presented a case study in which the right basal ganglia lesion resulted in LRO problems when the stimuli were presented in an allocentric reference frame (third person perspective), but not when presented in an egocentric reference frame (first person perspective). Thus, LRO for stimuli that need mental rotation seems to involve visuospatial abilities mediated by the right hemisphere.

There is evidence that not only visuospatial function, but also body related signals are important when stimuli are positioned in a third person perspective. Several studies found activation in brain areas involved in motor execution and planning when stimuli had to be mentally rotated to align the stimuli with the egocentric reference frame. For example, in laterality judgements tasks, participants are asked to identify the left or right hand of a line drawing (Parsons, 1987; Sekiyama, 1982). Participants mentally rotate their own hand into the stimulus's orientation to enable matching which demands input from the body related motor system. In turn, impairments of the motor system might affect performance on LRO tasks. For example, upper limb amputees' performance on a LRO is affected by the side of limb loss (Nico et al, 2004). That is, amputation of the dominant hand results in stronger LRO problems than amputation of the non-dominant hand. Similarly, individuals with congenital limb absence (Funk & Brugger, 2008), writer's cramp patients (Fiorio, Tinazzi, & Aglioti, 2006) and chronic pain patients (Coslett, Medina, Kliot, & Burkey, 2010; Moseley, 2004; Schwoebel, Friedman, Duda, & Coslett, 2001) show problems in deciding whether a corporeal stimulus is left or right, suggesting that afferent bodily signals are of paramount importance for LRO.

Yet, it is not clear which information of the body is crucial, this may vary from primary somatosensory and motor information to higher order representation of the body. Furthermore, it is not clear whether bodily information is important for stimuli viewed from a first person, from a third person, or from both perspectives. We aimed to investigate whether LRO with and without mental rotation can be selectively impaired after stroke. In addition, we investigated whether somatosensory (from primary to higher order) representations are related to impairments on LRO with and without mental rotation. Next, we performed a voxel-based lesion symptom mapping (VLSM) analysis. This analysis was conducted in a part of the sample, and was exploratory and assumption-free in nature, meaning that involvement of regions anywhere in the brain was assessed. By doing so, we aimed to assess the anatomical correlates of LRO, and to compare the anatomical substrate between the different subtests of the BRLD Test.

Methods

Patients

Patients with a unilateral first-ever supratentorial stroke were included. They met the following criteria: i) age of 18 years or older and admitted to the stroke unit of the Academic Hospital, ii) no other neurological or psychiatric condition apart from the stroke, iii) ability to communicate in Dutch, iv) no prior cognitive disorders that could hamper the validity of the test performance on the BRLD (for example, the diagnosis of a dementia, delirium or a depression). All patients had to be able participate in a neuropsychological examination for a minimum of 1h.

Diagnosis of a stroke was based on a clinical examination of a neurologist and was confirmed with CT-scanning or MR-imaging. During hospital stay, patients underwent a neuropsychological examination that included tests aiming at the somatosensory and body representation function and tests that measured attention & working memory, language and visuospatial neglect. The tests were conducted within 3 weeks post stroke. The neuropsychological examination was a part of standard work at the stroke unit (see *neuropsychological examination*).

Healthy controls

See table 1 for characteristics of the participants. Controls had no prior neurological disease nor were there indications of cognitive dysfunctions. Participants were recruited through advertisement and received a financial compensation. The neuropsychological examination was similar to the one that was conducted in the stroke patients. The experiment was performed in accordance with the declaration of Helsinki, and the protocol was deemed to be without psychological or medical risks, and complied with good ethical standards by the ethical advisory committee of the Faculty of Social and Behavioral Sciences at Utrecht University.

Table 1 | Characteristics of patients and healthy controls.

	Patients	Healthy controls
N	47	48
Male (%)	25 (53.2%)	22 (45.8%)
Age year (mean±SD)	61.5 ± 15.5	61.2 ± 9.0
Handedness (right)	42 (89%)	38 (79.2%)
Education Educational level* (mean±SD)	4.9 ± 1.0	4.7 ± 1.4

*Education levels categorised based on Verhage et al. (Verhage, 1964), a Dutch classification system including 7 categories. 1=did not finish primary school, 2=finished primary school, 3=did not finish secondary school, 4=finished secondary school, low level, 5=finished secondary school, medium level, 6=finished secondary school, highest level, and/or college degree, 7=university degree.

Neuropsychological examination

Left right orientation

We used the Bergen Right Left Discrimination Test (BRLD) to assess LRO (Ofte & Hugdahl, 2002). This is a test that has been commonly administered in experimental settings and consists of stickmen in different views of reference of which a participant has to indicate what the left or right hand of the stickmen is. It has been suggested that the subversions of the test measure LRO with and without mental rotation (Grewe, Ohmann, Markowitsch, & Piefke, 2014; K. Jordan, Wüstenberg, Jaspers-Feyer, Fellbrich, & Peters, 2006). The three conditions of the BRLD contain line drawings of stickmen, with two arms and a triangle that indicate the shoulders (see Figure 1). Stimuli consisted of stickmen that were either viewed from the back (first person perspective), the front (third person perspective) or alternating between back and front. Participants had to mark either the left or the right hand of each stickman, depending on the letter L or R that was printed below the stickman. Stickmen viewed from the front are regarded as stimuli that need mental rotation. That is, in order to determine what the left or right hand is, the participant need to either mentally rotate the image or make a shift from a first person to a third person perspective (Grewe et al., 2014). There are 48 figures in each subtest. The arms of the figures are drawn at different angles and positions related to its body. That is, arms are uncrossed, one arm crosses the vertical axis of the stickmen, or 2 arms cross the vertical axis of the stickmen. There are equal numbers of each arm position in the test. The participants had to mark as many stickmen as possible within 90 seconds. For the exact procedure see (Ofte, 2002). The primary outcome measure was an accuracy score, consisting of the percentage of correctly marked stickmen. The accuracy score was calculated for the three conditions, i.e. BRLD-Back, BRLD-Front and BRLD- Alternating. A BRLD-total score was calculated as the sum score of the three conditions.

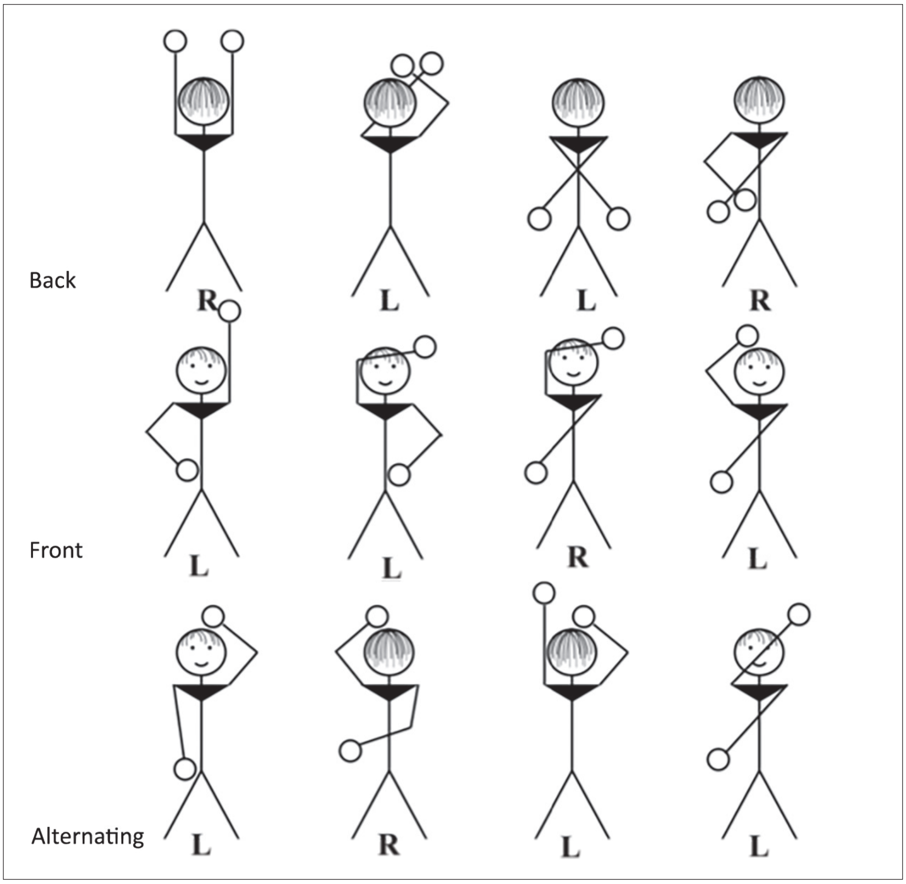

Figure 1 | Stimuli of the BRLD test.

Example of items of the BRLD test with three subtests: Back stimuli (first-person view), Front stimuli (third-person view) and Alternating stimuli. Each subtest was administered for 90 seconds; the outcome measure was based on the percentage correct score. In case the percentage correct score was 2SD below the mean, the performance was regarded as impaired. The BRLD-total score was the average score of all three conditions.

Predictors

The following 13 variables were a priori selected as predictors of BRLD performance. First, patient characteristics consisted of 1) gender, 2) handedness, 3) education and 4) affected hemisphere (stroke in left or right hemisphere) and 5) type of stroke (ischemic or haemorrhagic). Second, behavioural outcome measures of somatosensory function and body representation function were selected. Two questions concerning the subjective experience of somatosensory dysfunctions were included. That is, 6) whether the patient noticed problems in touch perception as a result of the stroke, i.e. “Did you experience difficulties in the perception of touch? (y/n)”. The other question concerned whether the patient noticed problems regarding the subjective sense of body ownership, i.e. 7) “Have you experienced the feeling that one of your limbs did not belong to yourself? (y/n)”. And if so, patients are asked which of the limbs(s) it concerns. For all patients who reported ownership problems, it related to the contralesional arm. In case patients did not fully understand the meaning of the question, the trained neuropsychologist provided additional information on touch perception and subjective sense of body ownership. Next, somatosensory functioning was examined by objective measures for the primary somatosensory function. That is, 8) touch perception and 9) proprioception. Touch perception was examined by administering 1 or 2 tactile stimuli on the fingers. Patients had to respond on how many stimuli (1 or 2) were felt (7 trials each hand, 14 in total). Proprioception was examined based on the proprioception subtest of The Rivermead Assessment of Somatosensory Performance (Winward et al., 2002) i.e. the direction proprioception of the thumb (10 movements for each thumb, 20 in total). Information on the structural body representation was measured by 10) finger gnosis. To examine finger gnosis, patients were asked to name the finger that had been touched, while blindfolded (7 trials each hand, 14 in total). Patients with bilateral primary somatosensory deficits (touch perception) did not perform the finger gnosis task. Patients with unilateral deficits were tested on the other (‘unaffected’) hand since finger agnosia has been regarded as a disorder that is bilaterally presented (Lezak 2004). Apart from predictors within the somatosensory and body representation domain, three tests aiming at other cognitive functions were included as well. First, language deficits are known to influence BRLD task performance since patients ought to discriminate between the letters L and R. Therefore, 11) language impairments were examined by the Boston Naming Task (Saxton et al., 2010)h. Next 12) attentional span and working memory, a function susceptible for cognitive harm, was examined by the digit span (back- and forward) of the Wechsler Adult Intelligence Scale III (Dutch condition) (Wechsler, 1987). Finally, 13) visuospatial neglect was measured by the Star

Cancellation Test (Halligan, Cockburn, & Wilson, 1991). Outcomes were transformed to categorical variables by setting a cut-off (impaired or unimpaired) (see Table 2).

Analyses

Neuropsychological examination

BRLD test performances of patients were transformed into z-scores based on the scores of the healthy control group. Patients performing with a z-score ≤-2 were labelled as impaired. As such, patients were divided in two groups, i.e. impaired and unimpaired. For BRLD performance, the outcome measure was the percentage correct score, that is number of correctly marked stickmen, divided by the total amount (correct + incorrect) stickmen. Patients had to mark a minimum of 5 items for the back condition, 3 items for the front condition and 3 items for the alternating condition in order to be included for analyses. This minimum total number of marked stickmen was set on 2SD below the mean of the performance of the patients. To analyse whether a difference exists between the patients and healthy controls on participant characteristics, a one-way ANOVA was conducted on age and educational level. For handedness, gender, side of stroke and type of stroke, the non parametric chi square test was conducted. To test whether a difference exists between the conditions (total, back, front and alternating), a mixed design ANOVA was conducted, with group (patients and controls) as a between subjects factor A forward logistic regression analysis was performed to examine the relationship between the BRLD test and the 13 predictors. Analyses were conducted for the BRLD-total score, BRLD-back, BRLD-front and BRLD-alternating condition. Outcome measures of the BRLD test as well as the 13 predictors were categorical, i.e. impaired or unimpaired (based on de z-scores). The predictors were entered into the model with a forward selection (LR) with a p value set on <.05. To test whether the patients included for VLSM analyses differed from the excluded patients, a one-way ANOVA was conducted on age and educational level. For handedness, gender, educational level, side of stroke and type of stroke, the non parametric chi square test. was conducted. Next, the logistic regression was repeated for the VLSM-group only, to verify if the behavioural results were in line with those of the total patient group.

Voxel-based Lesion Symptom Mapping

For the exact procedure on VLSM procedure, see (Biesbroek et al., 2014; Brink et al., 2016). In short, lesion maps were generated by manually delineating the lesion on either a CT of MRI scan by one reviewer who was blinded to neuropsychological data (JMB). The lesion maps were registered to the T1 MNI-152 (Montreal Neurological Institute) template (Fonov, Evans, McKinstry, Almli, & Collins, 2009). MRI scans were registered using elastix (Klein, Staring, Murphy, Viergever, & Pluim, 2010); CT scans were registered using a registration algorithm that was designed and validated for this purpose (Kuijf, Biesbroek, Viergever, Biessels, & Vincken, 2013). An intermediate CT/MRI template was used to enhance the quality of the registration procedure (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012). Quality checks were performed by comparing the original scan to the lesion map in MNI space by one reviewer who was again blinded to neuropsychological data and made manual adjustments if necessary (JMB). The procedure resulted in an accurate translation of the lesion maps to standard space in all cases. Regarding the statistics, VLSM analyses were performed with Non-parametric mapping (version December 2015, settings: Liebermeister) (Rorden, Bonilha, & Nichols, 2007). Four (binary) dependent variables were specified; impairments (y/n) on the BRLD total, back, front and alternating test. Voxels affected by ischemic lesions in less than 3 patients were not considered for analysis. Correction for multiple testing was achieved using the conservative Bonferroni familywise error correction ($p<0.05$).

Region of Interest-based stepwise regression analysis

To quantify the impact of regional lesion volumes, a Region of Interest (ROI)-based analysis was conducted. For this purpose, 96 cortical and 21 subcortical non-overlapping regions were extracted from the probabilistic Harvard-Oxford atlas (threshold at .25) (Desikan et al., 2006). Regions for subdivisions of gyri were merged into a single variable, thereby reducing the total number of regions to 89. For an elaborate description of this procedure, see Brink et al. (2016). An assumption-free approach was applied, meaning ROI's were not pre-selected beforehand. Instead, lesion volumes for all 89 ROI's were entered as independent variables in a Forward selection stepwise logistic regression model with the 4 binary outcome measures (impaired performance (y/n) on BRLD-total, BRLD-back, BRLD-front and BRLD-alternating) as dependent variables. The predictors were entered into the model with a p value set on <.05.

Results

The majority of the patients suffered from an ischemic stroke (42 patient, 89%), and 5 patients suffered from a hemorrhagic stroke. Of all patients, 24 (51%) had lesions in the right hemisphere. Patients were on average 61.5 years old (SD 15.5 years). For patient characteristics, see Table 1 and 4. In 32 patients, a MRI or CT scans were found to be suitable for a Voxel-Based Lesion Symptom mapping (VLSM) analyses. See *VLSM analyses* for more details. For the distribution of raw accuracy scores for the BRLD total performance of healthy participants and patients, see Figure 2. For average number of crossed stickmen and percentages correct, see Table 2. Six patients did not complete all tests and were therefore excluded from the regression analyses. For BRLD-total performance, healthy control subjects scored an average of 94.8% (±7.2) correct. For stroke patients, the average BRLD-total score was 84.4% correct (±15.9) Stroke patients showed an average accuracy of 86.6% on the BRLD-back condition, 84.8% on the BRLD-front and 81.6% in the BRLD-alternating condition. Patients performed significantly worse than control subjects on percentages correct $F(1,93)=1,43$ $p<.05$ but no differences between the subtests appear to be significant.

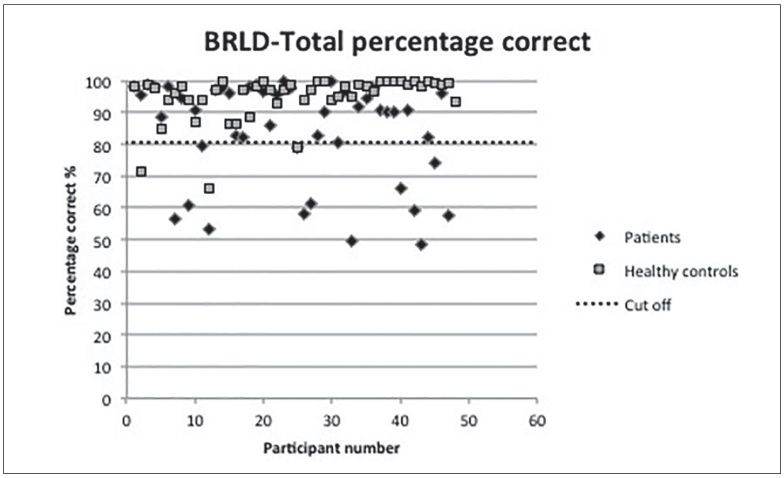

Figure 2 | Results of BRLD scores per participant. Scores represent the BRLD-total percentage correct scores of patients (n=47) and healthy controls HC (N=48). The dotted line represents 2SD below the mean score of the HC. Patients below this line are regarded as impaired.

Table 2 | Results of BRLD test. Numbers represent the absolute scores of the 4 outcome measures of the BRLD test for patients and healthy controls. Based on the healthy controls group, z-scores were formed and a cut-off was set for the percentage correct on 2 SD below the control mean.

	Healthy Controls		Patients		Cut-off for impaired performance
	Number of marked stickmen (mean ± SD)	Percentage correct (mean ± SD)	Number of marked stickmen (mean ± SD)	Percentage correct (mean ± SD)	Percentage correct
BRLD-total	96.5 ± 14.9	94.79 ± 7.22	56.49 ± 21.26	84.41 ± 15.87	80.35%
BRLD-back	34 ± 5.66	95.12 ± 8.10	21.72 ± 8.0	86.17 ± 16.65	78.92%
BRLD-front	32.40 ± 6.18	94.61 ± 8.00	19.2 ± 8.48	84.79 ± 21.10	78.61%
BRLD-alternating	30.13 ± 5.42	94.29 ± 8.66	16.83 ± 6.87	81.64 ± 18.95	76.97%

BRLD impairments

For the BRLD-total score, 13 out of 47 patients were found to be impaired (28%) (see Table 3). Zooming in on the three conditions, 25 patients (53.2%) were unimpaired for all three conditions. Six patients (12.8%) were impaired for all three conditions. 11 patients (23.4%) were impaired on BRLD-back, of whom 10.6% (5 patients) were unimpaired on the BRLD-front and 8.5% (4 patients) were unimpaired on the BRLD-alternating task. For patients who were impaired on the BRLD-front, only 3 patients (6.4%) were unimpaired on the BRLD-alternating. Of the 15 patients that were impaired in the BRLD-alternating, 5 were unimpaired on the BRLD-front task. See Table 3 and Figure 2 for all details.

Table 3 | Impairments on the BRLD subtests. Cross table that show the percentages of impairments within the patient group on the three condition of the BRLD task. Impairments were based on the healthy control group (2SD below the mean). Impairments were most frequent on the BRLD-alternating condition (31.9% of the patients) followed by the BRLD-front condition. Note that patients could be impaired on the BRLD-back but not on the BRLD-front or vice versa.

Percentages of impairments on three conditions		BRLD-alternating					
BRLD-back	**BRLD-front**	**Unimpaired**		**Impaired**		**Total**	
Unimpaired		28	59.6%	8	17.0%	36	76.6%
	Unimpaired	25	53.2%	4	8.5%	29	61.7%
	Impaired	3	6.4%	4	8.5%	7	14.9%
Impaired		4	8.5%	7	14.9%	11	23.4%
	Unimpaired	4	8.5%	1	2.1%	5	10.6%
	Impaired	–	–	6	12.8%	6	12.8%
Total		32	68.1%	15	31.9%	47	100.0%

Predictors

BRLD-total

Logistic regression found that finger agnosia contributed significantly to BRLD-total performance. That is, patients who showed impairments on the finger gnosis task were significantly more impaired on BRLD-total than patients without finger gnosis deficits, B 2.95, Exp (B) .54 p<.02 (see also Figure 3). Regarding the other cognitive functions, visuospatial neglect significantly contributed to BRLD-total performance B 3.44, Exp (B) .32 p<.01. That is, patients suffering from neglect showed more incorrect items on the BRLD-total performance as opposed to patients without neglect.

BRLD-back

Regarding the BRLD-back percentage correct; visuospatial neglect predicted performance strongest B 2.78, Exp (B) .062 p<.01. Taking neglect out of the model, BRLD-back performance was strongest predicted by subjective touch impairment B 1.946, Exp (B) 1.43 p<.05. That is, patients who reported problems in touch perception performed worse than patients who did not report touch perception impairments. None of the other predictors were related to BRLD-back performance.

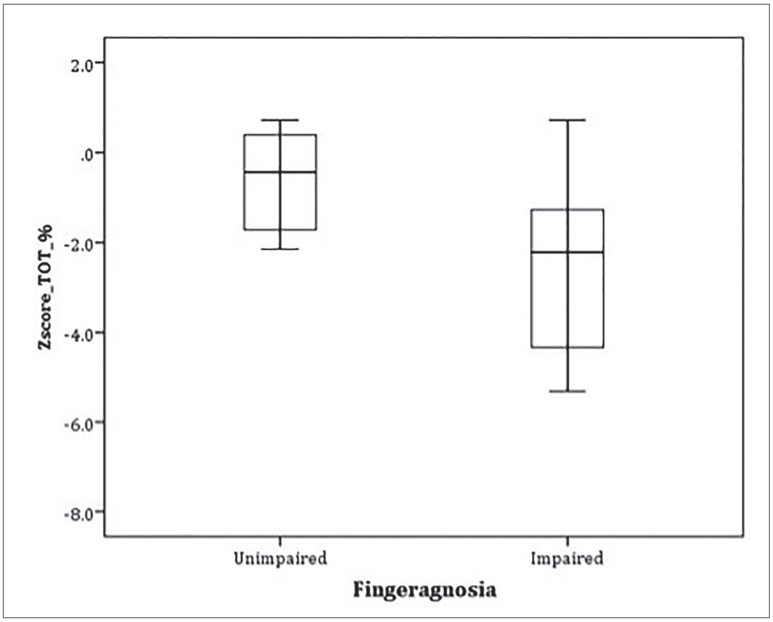

Figure 3 | Results of BRLD total z-scores. Boxplot represents z-scores of BRLD-total test patients of patients with and without impairments on the fingergnosis test. Patients with an impairment on the finger gnosis test were likely to be impaired on the BRLD-total score.

BRLD-front

Regarding the BRLD-front percentage correct, subjective sense of body ownership impairments contributed to BRLD-front impairments B 3.22, Exp (B) .04 $p<.02$. That is, patients that reported body ownership deficits had a higher chance of showing impairments in BRLD-front task. In addition, finger agnosia significantly predicted BRLD-front impairments B 1.85, Exp (B) .16 $p<.05$. Visuospatial neglect trended towards significance B 2.18, Exp (B) .11 $p=.051$. None of the other predictors were related to BRLD-front performance.

BRLD-alternating

For BRLD-alternating performance, proprioceptive impairments predicted percentage correct impairments B=2.56 Exp (B) .11 $p<.02$. In addition, gender was trending towards significance, meaning that women were less accurate than men B=1.69 Exp (B) .19 $p=.06$. In order to assess which predictors were related to the switching between the front and back stimuli, the BRLD-alternating performance was corrected for the BRLD-back condition. For this score, attention and working memory was the only predictor that was found to be significant B=1.95 Exp (B) 0.14 $p<.05$, suggesting that this predictor was related to the mental switching between back and front.

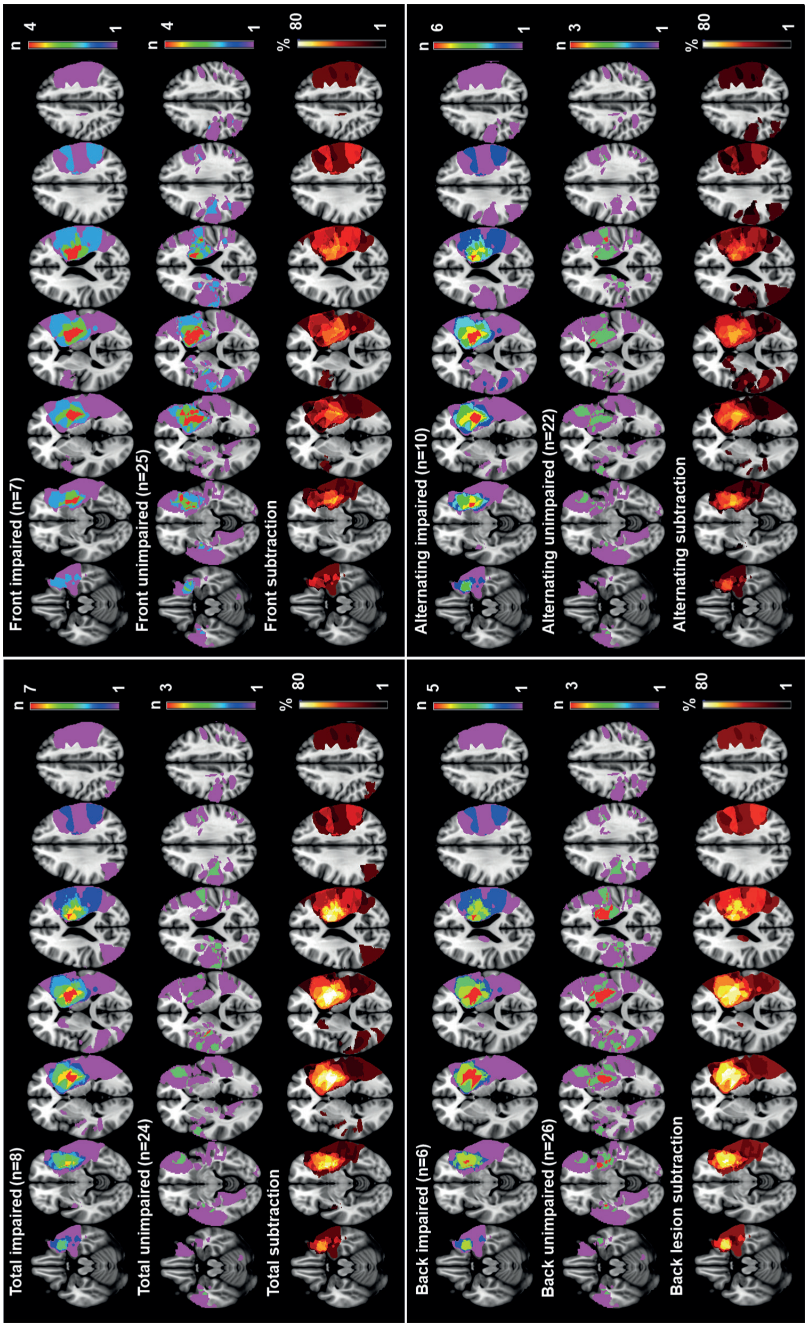

Figure 4 | Lesion subtraction plot. Lesion subtraction plot of patients with impaired and unimpaired performance on the BRLD-total. In each box, the overlay plots (upper and middle rows) show the number of patients with a lesion for a given voxel separately for patients with impaired and unimpaired performance. The lesion subtraction plot shows which voxels are more often damaged in patients with impaired performance compared to patients with unimpaired performance (absolute difference in %). For example, the subtraction plot for BRLD-total performance shows that the absolute difference in lesion prevalence in the right striatum and insula is approximately 80% (with the insula and striatum being more often affected in patients with impaired performance).

7

Neuroanatomical correlates (VLSM)

Behavioral data

The behavioral data as well as patient characteristics did not significantly differ between the whole group (n=47) and the selected VLSM group (n=32) which suggests that the VSLM subgroup is representative for the whole group. This concerned age, handedness, gender, educational level, side of stroke and type of stroke. Moreover, results of the regression analysis of the VLSM subgroup were in line with the total group, again suggesting that the VLSM subgroup was a representative sample of the whole group.

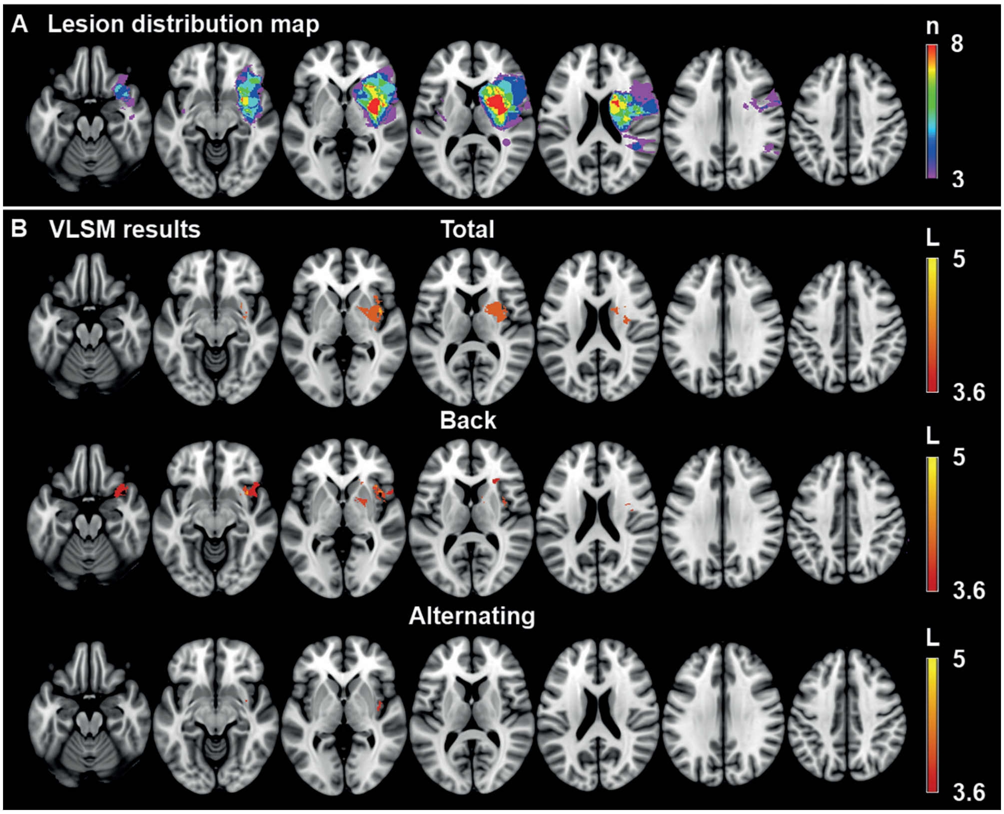

Figure 5 | a): Lesion distribution map. Voxels that are damaged in at least three patients are projected on the 1 mm MNI-152 template. Colours indicate the number of patients with a lesion for each voxel. The majority of damaged voxels are located in the right hemisphere. b): Voxel based lesion symptom mapping results. Voxels with a statistically significant association (Liebermeister statistic) between the presence of a lesion and impairment on left right orientation tasks are shown on a scale from red to yellow. Results are corrected for multiple testing (Bonferroni FWE p<.05). For the BRLD-total, -back and -alternating condition, lesions in the right insula was associated with impairments, as can be appreciated from this figure. For the BRLD-front condition, no significant voxels were found.

Lesion subtraction

Lesion overlay and subtraction plots of patients with impaired and unimpaired performance on the BRLD test are shown in Figure 4. The right insula and right striatum were far more often affected in patients with impaired performance than unimpaired patients, suggesting a crucial role of these regions in left right orientation.

Voxel-based lesion-symptom mapping

VLSM analyses identified clusters of voxels with a statistically significant association between the presence of a lesion and BRLD impairments (Figure 5). These voxels were mostly located in the right insular cortex. For the back and alternating subversions of the test, a similar pattern was found with significant voxels located predominantly in the right insular cortex. For the BRLD-front condition, none of the voxels were significantly associated with impairment after correction for multiple testing.

Region of Interest-based stepwise regression analysis

For BRLD-total, BRLD-back and BRLD-alternating impairments, a statistically significant effect was found for the right insula cortex [BRLD-total B=.847 Exp (B) 2.33 p<.01, BRLD-back B=.635 Exp (B) 1.89 p<.01 and BRLD-alternating B=.47 Exp (B) 1.6 p<.01]. None of the remaining regions contributed to the model, nor did total infarct volume. For BRLD-front impairment, lesions within right insula cortex predicted performance as well B=.506 Exp (B) 1.658 p<.01, in addition to the left precentral gyrus B=1.52 Exp (B) 4.55 p<.05.

Discussion

In the current study we aimed to elucidate the occurrence of left-right orientation (LRO) deficits shortly after stroke, it's predictors and neural correlates. We found that patients can be selectively impaired on different aspects of left-right orientation (LRO) since patterns of double dissociations between the subtests are found. That is, patient could be selectively impaired in LRO for stimuli placed in a first person perspective, a third person perspective or when switching between those two was required. Second, body representation impairments are a strong predictor of the total (sum) score of the test, as well as the subtest for third person perspective stimuli. Left right orientation in a first person perspective was less strongly predicted by body representation deficits. Switching between first and third person perspective was predicted by proprioceptive impairments as well as attention and working memory. A third finding is that abnormalities of LRO are associated with lesions in the right insular cortex. This was found consistently across all conditions and was supported by a regression analysis that showed that lesion volume within the insular cortex was strongly associated with LRO impairments.

These three findings demonstrate a link between LRO, the somatosensory system and the insular cortex. This specifically shows that the higher order aspects of the somatosensory processing, those involved in body representation, are required to distinguish left from right. Previous studies have found that primary sensorimotor functioning is important for LRO; these studies demonstrated that the sensorimotor function generates an update of the position of our own body or body parts, in order to match this information to the visual stimulus (Ionta & Blanke, 2009; Ionta, Fourkas, Fiorio, & Aglioti, 2007; Parsons, 1987; Shenton, Schwoebel, & Coslett, 2004). Our results suggest that higher order aspects of the somatosensory system are also involved in LRO. In the current study, body representation deficits consisted of structural body representation deficits (as measured by finger gnosis) as well as subjective body ownership deficits (as measured by subjective reports). Finger agnosia has been traditionally linked to LRO impairments in relation to Gerstmann syndrome. However, our study did not find a relation between finger agnosia and LRO per se, but only for stimuli in which a third person perspective has to be taken. In addition, subjective sense body ownership also showed a robust relation with LRO for third person perspective stimuli. A possible explanation would be that taking a third person perspective demands motor- and visual imagery (Brady, Maguinness, & Choisdealbha, 2011; Choisdealbha, Brady, & Maguinness, 2011; Conson, Mazzarella, Donnarumma, & Trojano, 2012) and this may be hindered by problems in recognizing or feeling your hand as your own. Taking a third person perspective requires a high cognitive demand as information from different modalities have to be integrated and translocated to another person's perspective (Blanke, Ortigue, Landis, & Seeck, 2002; Vogeley & Fink, 2003). Perhaps this process is hindered by impairments in higher order aspects of somatosensory processing which is exemplified by the deficits in finger gnosis and the subjective sense of body ownership complaints in the current study. This is in line with a recent study in stroke patients who suffer from body awareness problems (Besharati et al., 2016). This study investigated patients with and without anosognosia for hemiplegia (body awareness problems) on their ability to take a third person perspective. Results show that patients with anosognosia for hemiplegia exhibited more deficits in taking the third person perspective that positively correlated with the severity of body awareness. Other studies have found a link between body ownership and perspective taking as well. For example, symptoms of body ownership impairments were reduced when patients viewed one's affected arm through a conventional mirror (Fotopoulou et al., 2011; Jenkinson, Haggard, Ferreira, & Fotopoulou, 2013). Therefore, the body ownership impairments were only present when viewing the affected arm from a first person, and not a third person perspective. Although this study also demonstrates a link between body ownership and perspective taking, there are a few discrepancies with our current study. First, our patients who reported problems in the sense of ownership did not all suffer from somatoparaphrenia as in the study of Fotopolou and colleagues (Fotopoulou et al., 2011; Jenkinson et al., 2013) in which a complete denial and rejection of ownership is present. In the current study, patients with body ownership problems were diagnosed when patients subjectively reported having problems in recognizing or feeling as if their hand belongs to themselves. Second, the study of Fotopoulou and colleagues showed that body ownership impairments are reduced by taking a third person perspective, while the current study show an opposite causal relationship, that is; taking a third person perspective is hindered when body ownership impairments are present. Together, these results suggest that perspective taking and body representation are tightly connected, but that the direction of their relation is equivocal. Another cue to the connection between spatial orientation and body representation comes from the finding that the right insula seems to be an important area to mediate these functions. An interesting line of research on this topic involves stimulation of vestibular input on spatial cognition and body representation (for review see Lopez, 2016). Caloric vestibular stimulation (CVS) or galvanic vestibular stimulation (GVS), stimulates the vestibular nerve through transcutaneous electrical current, while the head remains stationary. Stimulation of this network is associated with a wide range of sensorimotor as well as cognitive functions. Importantly, GVS reduces symptoms of visuospatial neglect and somatoparaphrenia (Bisiach, Rusconi, & Vallar, 1991; Rode et al., 1992; Salvato et al., 2016) as well as other body related disorders (Bottini, Gandola, Sedda, & Ferrè, 2013; Gandola et al., 2014; Lopez, 2016b). Although the exact locations and functions of vestibular cortical areas are still a matter of debate, there is a wide agreement that the insular cortex plays a central role (Lopez, 2016b; Lopez & Blanke, 2011). The current study may therefore reflect a similar mechanism in which the insular cortex is associated with body representation impairments as well as spatial (left right) orientation.

Three limitations of the current study should be mentioned. Our study population is probably not representative for the stroke population in general. Patients who could be examined for a minimum of one hour within the first three weeks post stroke (average of 6 days) may be less affected by the stroke than the average stroke patient. Therefore, the prevalence of LRO impairments in this group might be an underestimation of the genuine prevalence in the population. Second, with regards to the notion that body representation deficits predict LRO impairments, one explanation for this relation might be that patients with somatosensory or body representation impairments are more affected by stroke in general, and are therefore also more impaired on other tasks such as the BRLD task. However, this explanation is not likely for three reasons. First, the relationship between body representation and BRLD impairments only manifests in the BRLD-total, the BRLD-back and the BRLD-front conditions but is not apparent in the BRLD-alternating condition. As this latter condition is the most cognitively demanding subtask (Grewe et al. 2014), it is unlikely that this result is a function of severity of the stroke. Second, attention and working memory, a cognitive function susceptible for general cognitive harm, did not significantly correlate with body ownership impairment, nor did they significantly predict BRLD outcome except when isolating the switching component of the BRLD-alternating test. Third, ROI analysis did not find an association with total infarct volume and impaired performance. Therefore, somatosensory and body representation deficits might be genuinely modulating BRLD performance and not be explained by the severity of the stroke and its consequences.

A third limitation pertains to the VLSM analysis. The lesion frequency in the left cerebral hemisphere is relatively low (despite the substantial number of patients with left hemispheric lesions). One of the reasons is that patients with severe to global aphasia were not able to comprehend task instruction and the BRLD test was therefore not administered and patients were not included in the current study. As a consequence, most voxels in the left cerebral hemisphere were not included in the VLSM analysis. Therefore, we cannot draw any strong conclusions regarding the interhemispheric lateralization of LRO and body representation. Similarly, the lesion frequency of the posterior parts of the brain, including the occipital and posterior parts of the parietal cortex was low, which resulted in a low power to detect associations with LRO. Although the effect for the right insula was highly significant, this finding should be interpreted with caution. That is, the insula may not be the only area involved in LRO. Finally, the number of patients included for VLSM analyses was substantially lower than for the analysis of the behavioural data. This was largely due to the CT of MRI scan that was not suitable for analysis. However, the behavioural data as well as patient characteristics did not significantly differ between the whole group (n=47) and the selected VLSM group (n=32) that suggests that the VSLM group is representative for the whole group.

To conclude, the current study shows that LRO can be selectively impaired for stimuli in a first-person and third person perspective. Body representation impairments are associated with impairments in LRO for stimuli viewed from a third person perspective. Impairments with LRO are associated with lesions in the right insula cortex. These findings suggest that the right insular cortex may be involved in a network that represents both perspective taking and body representation.

Acknowledgements

We thank Miranda Smit, Nathan van der Stoep, Lieke Makkinga and Jasmijn Berkhof for their help in collecting the data.

Table 4 | Characteristics of patient group for demographic and behavioural results. Each line represents each patient. The + indicates a positive results. That is, the first patients is included for VLSM analysis, suffers from subjective touch impairments, but not (-) from body ownership impairments. In addition, is does not show any impairments on the neuropsychological assessment nor on the BRLD test.

Included for VLSM analysis	Age (years)	Gender	Educational level*	Affected hemisphere	Type of stroke	Handed-ness	Subjective touch impair-ments	Subjective body ownership impairments	Visuospatial neglect	Language impairment	Attention & Working memory	Proprio-ception	Touch perception	Finger-agnosia	BRLD -total	BRLD -back	BRLD -front
									≥1 incorrect (lateralised)	Cut-off: <5th per-centile	Cut-off: <5th per-centile	Cut-off:: ≥1 incorrect	Cut-off: ≥1 incorrect	Cut-off: ≥2 incorrect	Cut-off: <80.35% correct	Cut-off: <78.92% correct	Cut-off: <78.61% correct
1 +	70	f	6	r	ischemic	r	+	-	-	-	-	-	-	-	-	-	-
2 +	37	m	5	l	ischemic	r	-	-	-	+	+	-	-	-	-	-	-
3 +	56	f	4	l	ischemic	r	-	-	-	-	-	-	-	-	-	-	-
4 +	63	f	3	l	ischemic	r	+	-	-	-	-	-	-	-	-	-	-
5 +	84	m	5	l	ischemic	l	-	-	-	-	+	-	-	+	-	-	+
6 +	57	m	6	l	ischemic	r	-	-	-	+	+	+	-	-	-	-	-
7 +	66	m	5	r	ischemic	r	-	-	+	-	-	+	-	+	+	+	+
8 +	54	m	5	r	ischemic	r	+	-	+	-	-	+	+	-	-	-	-
9 +	48	f	4	r	ischemic	r	+	-	-	-	-	+	-	+	+	+	-
10 +	76	f	4	l	ischemic	r	-	-	-	-	+	-	-	-	-	-	-
11 +	75	f	x	x	ischemic	x	-	-	+	x	x	+	-	-	+	+	-
12 -	84	f	5	r	ischemic	r	-	-	-	x	-	-	-	-	+	+	+
13 +	79	f	6	l	ischemic	r	-	-	-	+	-	-	-	-	-	-	-
14 +	46	m	5	l	ischemic	r	+	-	-	-	-	+	+	-	-	-	-
15 +	66	m	7	r	ischemic	r	-	-	-	-	-	-	-	-	-	-	-
16 -	84	m	2	r	ischemic	r	-	-	-	-	-	-	-	+	-	-	-
17 -	78	f	5	r	ischemic	r	+	+	-	-	-	+	-	+	-	-	+

Table 4 | *Continued*

Included for VLSM analysis	Age (years)	Gender	Educational level*	Affected hemisphere	Type of stroke	Handed-ness	Subjective touch impairments	Subjective body ownership impairments	Visuospatial neglect	Language impairment	Attention & Working memory	Proprio-ception	Touch perception	Finger-agnosia	BRLD -total	BRLD -back	BRLD -front
									≥1 incorrect (lateralised)	Cut-off: <5th per-centile	Cut-off: <5th per-centile	Cut-off:: ≥1 incorrect	Cut-off: ≥1 incorrect	Cut-off: ≥2 incorrect	Cut-off: <80.35% correct	Cut-off: <78.92% correct	Cut-off: <78.61% correct
18 +	49	m	6	l	ischemic	r	+	-	-	-	-	-	-	-	-	-	-
19 +	61	m	6	r	ischemic	r	-	-	-	-	-	-	-	-	-	-	-
20 +	56	m	6	r	ischemic	r	-	-	-	-	-	-	-	-	-	-	-
21 +	48	f	4	l	ischemic	r	-	-	-	x	x	-	-	-	-	-	-
22 -	69	m	6	l	ischemic	r	+	-	-	-	-	+	-	+	-	-	-
23 +	64	f	5	r	ischemic	l	-	-	-	-	-	-	-	-	-	-	-
24 +	49	f	5	r	ischemic	r	-	-	-	-	-	-	-	-	-	-	-
25 +	69	m	4	l	ischemic	r	-	-	-	-	-	-	-	+	+	-	+
26 +	69	f	3	r	ischemic	r	-	+	+	-	-	+	+	-	+	-	+
27 -	72	f	4	l	ischemic	r	+	+	x	-	-	-	-	+	+	+	+
28 +	46	f	4	l	ischemic	r	+	-	-	-	+	-	-	-	-	+	-
29 -	33	m	6	l	ischemic	r	+	-	-	-	-	+	+	-	-	-	-
30 +	66	m	5	l	ischemic	r	-	-	-	-	-	-	-	+	-	-	-
31 -	55	m	4	r	hemorrhagic	r	+	-	+	-	-	+	+	-	-	+	-
32 -	80	m	5	r	ischemic	r	-	-	-	-	-	-	-	-	-	-	-
33 -	49	f	5	r	hemorrhagic	r	+	+	+	-	-	+	+	-	+	+	+
34 -	85	f	5	r	hemorrhagic	r	+	-	-	-	-	-	x	-	-	-	-
35 -	49	m	5	r	ischemic	r	-	-	x	-	-	-	+	x	-	-	-

Table 4 | *Continued*

Included for VLSM analysis	Age (years)	Gender	Educational level*	Affected hemisphere	Type of stroke	Handed-ness	Subjective touch impairments	Subjective body ownership impairments	Visuospatial neglect	Language impairment	Attention & Working memory	Proprio-ception	Touch perception	Finger-agnosia	BRLD -total	BRLD -back	BRLD -front
									≥1 incorrect (lateralised)	Cut-off: <5th per-centile	Cut-off: <5th per-centile	Cut-off:: ≥1 incorrect	Cut-off: ≥1 incorrect	Cut-off: ≥2 incorrect	Cut-off: <80.35% correct	Cut-off: <78.92% correct	Cut-off: <78.61% correct
36 +	71	m	5	l	ischemic	l	-	-	-	-	-	-	-	-	-	-	-
37 -	87	f	5	l	ischemic	r	-	x	x	-	-	-	-	-	-	-	-
38 +	83	m	5	l	ischemic	r	-	-	-	-	-	-	-	-	-	-	+
39 -	27	m	5	r	hemorrhagic	r	+	+	-	+	-	-	+	-	-	-	-
40 +	48	f	3	r	ischemic	r	-	-	-	+	+	-	-	+	+	-	+
41 +	58	m	6	l	ischemic	r	+	-	-	-	-	+	+	-	-	-	-
42 +	43	f	6	r	ischemic	l	+	-	+	-	-	-	+	-	+	+	+
43 -	41	f	5	l	ischemic	r	+	-	-	+	+	+	-	-	+	-	+
44 -	46	m	5	l	hemorrhagic	r	-	-	-	+	-	-	-	-	-	+	-
45 +	75	m	4	l	ischemic	l	-	-	-	-	+	+	-	+	+	-	-
46 +	74	f	7	r	ischemic	r	-	-	+	-	-	-	-	-	-	-	-
47 +	45	m	4	r	ischemic	r	+	+	+	-	-	+	+	-	+	+	+

7

Chapter 8

No consistent cooling of the real hand in the rubber hand illusion

A.M. de Haan
H.E. Van Stralen
M. Smit
A. Keizer
S. van der Stigchel
and
H.C. Dijkerman

As published in: Acta Psychologica, 179, 68-77 (2017).

A.M.H, H.E.S., S.S., and H.C.D. designed research. A.M.H., H.E.S, M.S., and A.K. performed research. A.M.H. analysed data. A.M.H., H.E.S, M.S., A.K., S.S., and H.C.D. wrote the paper.

Abstract

In the rubber hand illusion (RHI), participants view a rubber hand that is stroked synchronously with their real, hidden hand. This procedure results in experiencing an increased sense of ownership over the rubber hand and demonstrates how multisensory information (vision, touch) can influence the sense of body ownership. However, it has also been suggested that a (lack of) sense of ownership over an own body part may in turn influence bodily processes. This suggestion has previously been supported by the observation that a decrease in skin temperature in the real hand correlated with ownership over the rubber hand. However, this finding has not been consistently replicated. Our lab has conducted several studies in which we recorded temperature of the hands during the RHI using various measures and in different circumstances, including continuous temperature measurements in a temperature-controlled room. An overall analysis of our results, covering five attempts to replicate the traditional RHI experiment and totalling 167 participants, does not show a reliable cooling of the real hand during the RHI. We discuss this failure to replicate and consider several possible explanations for inconsistencies between reports of hand temperature during the RHI.

Introduction

Consider a simple task such as walking towards another person – say, this huge big shot you noticed at a conference – and shaking hands. Your brain is charged with the challenging mission of walking, while making an appropriate arm movement, without knocking other things over, shaking the wrong hand, colliding forcefully with the target hand, or crushing it if you managed to reach it without accidents. Also, among this sea of moving limbs you will need to keep track of which ones are yours, so you can walk away again without making a complete fool out of yourself. To do so, your brain needs to know which parts of the world are "you" and which parts are not. To no surprise, the concept of body ownership, or recognition that your body indeed is your own, has received ample attention (De Vignemont, 2011; Henrik Ehrsson, Spence, & Passingham, 2004; Kilteni, Maselli, Kording, & Slater, 2015; Serino et al., 2013; Tsakiris, 2010, 2016; Tsakiris, Hesse, Boy, Haggard, & Fink, 2007b).

While body ownership is considered a basic part of the sense of the self (Blanke, 2012; Gallagher, 2000; Serino et al., 2013), various illusions have shown that body ownership is surprisingly malleable (Alimardani, Nishio, & Ishiguro, 2016; Botvinick & Cohen, 1998; Henrik Ehrsson, 2007; Newport, Pearce, & Preston, 2010; Petkova & Ehrsson, 2008; Slater, Spanlang, Sanchez-Vives, & Blanke, 2010; van der Hoort, Guterstam, & Ehrsson, 2011). In these illusions, healthy participants are made to believe that an artificial object (Botvinick & Cohen, 1998; Ma & Hommel, 2015; Pasqualotto & Proulx, 2015) (or even artificial body such as a complete mannequin) (Maselli & Slater, 2013; Petkova & Ehrsson, 2008; Petkova, Khoshnevis, & Ehrsson, 2011; Salomon, Lim, Pfeiffer, Gassert, & Blanke, 2013; Slater et al., 2010) is part of their body by providing "false" multisensory information. In the most widely used version, the rubber hand illusion (RHI), a rubber hand is being stroked synchronously with one's own unseen hand. This causes integration of the visual and tactile input about the stroking which is felt on the rubber hand. This leads to the experience that the rubber hand feels like the own real hand (Botvinick & Cohen, 1998). Apart from the subjective changes assessed with questionnaires, the estimated position of the real hand is drifted towards the rubber hand (proprioceptive drift).

This illusion reveals that the brain's ability to integrate bottom-up multisensory input (vision, touch) heavily influences the sense of body ownership. Interestingly, gaining ownership of a foreign hand has consequences for the perception of the own "replaced" hand. Indeed, it has been suggested that the hand for which the illusion is evoked is somewhat disowned. This may in turn influence various physiological processes. For example, Barnsley et al. (Barnsley et al., 2011) showed that histamine reactivity was increased after conducting the RHI, an effect that was only present for the stimulated, "replaced" arm. Hegedüs et al. (Hegedüs et al., 2014) reported higher pain thresholds of the real hand after RHI induction (although it should be noted that Mohan et al. (Mohan et al., 2012) did not find any influence on pain ratings of noxious heat stimuli). Moreover, it has been suggested that the RHI leads to slower processing of tactile stimuli on the “replaced” arm (Moseley et al., 2008).

One influential and widely cited effect of the RHI is a drop in skin temperature for the replaced own hand (Moseley et al., 2008). Moseley et al. (Moseley et al., 2008) observed that many pathological conditions (e.g. anorexia nervosa, complex regional pain, stroke) are characterised by both body ownership problems and a disturbed thermoregulation. They hypothesised that these symptoms are related, which could explain why disruption of temperature regulation can be restricted to a specific limb. This would imply that body ownership is not only a cognitive phenomenon that arises from having to control a body and bodily processes, but may in turn influence physiological processing in the body. Using the traditional RHI, Moseley et al. (Moseley et al., 2008) showed a relative decrease in skin temperature in the real “replaced” hand of about 0.2–0.8°C that correlated with ownership over the rubber hand. Most importantly, in their Experiment 3 they compared synchronous with asynchronous stroking and showed that the hand temperature after a 7–8 minute stroking period was lower with synchronous than with asynchronous stroking on the test hand, whereas no difference was found on the non-stimulated hand. This suggests that the cooling is related to the illusionary disowning of the real hand in favour of the rubber substitute.

However, replication of this effect has been inconsistent. To our knowledge, since the study by Moseley and al (Moseley et al., 2008), eight studies have published results on hand temperature measurements during the traditional RHI in healthy participants (David, Fiori, & Aglioti, 2014; Grynberg & Pollatos, 2015; Kammers, Rose, & Haggard, 2011a; Paton, Hohwy, & Enticott, 2012; Rohde, Wold, Karnath, & Ernst, 2013; Thakkar, Nichols, McIntosh, & Park, 2011; Tsakiris, Tajadura-Jiménez, & Costantini, 2011; Van Stralen et al., 2014). Only three of them could replicate the RHI related temperature drop. Kammers et al. (Kammers, Rose, & Haggard, 2011a) showed a relative cooling of the hand in synchronous compared to asynchronous conditions in the RHI. They provide additional evidence for the link between the RHI and local temperature changes, as artificially lowering the hand temperature increased proprioceptive drift in the RHI, while increasing the hand temperature decreases proprioceptive drift. Hand temperature manipulation did not influence subjective ratings of body ownership, but it has been shown before that proprioceptive drift and body ownership questionnaires measure different aspects of the RHI (Abdulkarim & Ehrsson, 2016; Blanke, 2012; Fiorio et al., 2011; Rohde, Luca, Ernst, Di Luca, & Ernst, 2011). Tsakiris et al. (Tsakiris et al., 2011) also found a lower hand temperature in synchronous compared to asynchronous stroking in the RHI, however only in participants with relatively low interoceptive sensitivity, and it appeared to be more related to the proprioceptive drift outcomes than the subjective ratings of the RHI. Also, hand temperature change only showed a very small correlation with the level of interoceptive sensitivity, so it seems not entirely clear what was causing most of the temperature change in this experiment. Finally, a study from our lab (Van Stralen et al., 2014) reported a RHI-related hand temperature drop with slower stroking velocities in the RHI, which elicit an affective touch sensation and increases the effect of the RHI. However, a second experiment in the same study and using the same methods, did not replicate the temperature change (while it did replicate the increase in proprioceptive drift with slower stroking). This therefore might suggest that affective, pleasant stoking may be linked to temperature changes of the hand. Indeed, literature on affective touch shows that stroking with a velocity around 3cm/s activated C-tactile fibers that project to the posterior insula and is associated with a pleasant feeling. Interestingly, the posterior insula has also been linked to interoception, for instance of body temperature (Craig et al. 2002).

In studies using variations on the RHI or related bodily illusions, skin temperature drop has also occasionally been replicated. Hohwy et al. (2010) showed a hand temperature change related to the synchrony of stroking using some variants of the (in this case virtual) rubber hand illusion, but did not find any temperature changes in other variations on the RHI (although these variations did elicit the changes in sense of ownership). Salomon et al. (2013) found a very small temperature decrease of on average around 0.010–0.015^{o}C after about half a minute of stroking (see their supplementary Figure S1) on the leg and back in congruent conditions of a full body illusion, in which illusionary ownership over a complete fake body was generated by the use of a virtual reality setup. Macauda et al. (2015) used visual and vestibular input to create a full body illusion and also reported a small but significant drop in hand and neck temperature in the congruent full body illusion condition.

However, many other studies report a failure of replication of the temperature drop in the RHI either finding no temperature changes, or temperature changes that are independent of stroking synchrony, so unrelated to the illusion of body ownership. Paton et al. (Paton et al., 2012) found no cooling of the test hand in the RHI using sensitive temperature measurements (0.01°C accuracy, 2 Hz sampling over 15 seconds) in either participants with autism spectrum disorder or healthy controls. Grynberg & Pollatos (Grynberg & Pollatos, 2015) also found no relative cooling of the hand in the RHI in a study investigating possible links between RHI susceptibility and lower awareness of emotional and non-emotional internal bodily signals. Other studies did find a drop in hand temperature, but independent of the synchronicity of stroking (David et al., 2014; Thakkar et al., 2011). A case study in our lab in a patient with problems in ownership of her left arm showed a temperature drop in the left arm as a result of the RHI procedure but not in the right arm, but this was again independent of stroking synchronicity (van Stralen et al., 2013). One study specifically set out to investigate the relative cooling of the test hand in the RHI. Rohde et al. (Rohde et al., 2013) used a robot arm to apply the stroking and did not find any temperature changes over the course of a 3.3 minute stroking period, nor after 5-7 minutes of continuous stroking, while subjective ratings of the illusion and proprioceptive drift were in the range generally reported in RHI literature. When reverting to manual stroking and mimicking the procedure of Moseley et al. (Moseley et al., 2008) as closely as possible, Rohde et al. (Rohde et al., 2013) found a significant drop in hand temperature of the stimulated hand, but this drop was independent of synchronicity of stroking (although there was a trend) and did not correlate with vividness of the illusion. Also, subjective ratings of the illusion and proprioceptive drift did not differ between the automatically applied and manually applied conditions. Therefore, the authors suggested that uncontrolled low level properties of the stimuli applied in the traditional RHI rather than subjectively felt ownership may cause temperature changes in some studies but not others.

Overall, these studies raise the question whether hand temperature really is a reliable objective measure of hand disownership during the RHI, especially given the known publication bias for positive findings (Franco, Malhotra, & Simonovits, 2014). Unfortunately, the literature that reports hand temperature in the rubber hand illusion in healthy participants is limited and quite diverse in their analyses and coverage, making a meta-analysis problematic. Over the years, several studies in our lab have included hand temperature as a dependent variable in their design. As mentioned above, we did find an effect of the RHI on hand temperature in one experiment (Van Stralen et al., 2014). Other studies in our lab have recorded temperature of the hands during the RHI with various measures and in different circumstances, but on a single study level did not find any illusion-related changes in hand temperature. This made us question the reliability of hand temperature as a measure of body disownership in the RHI and we therefore performed a RHI study in a temperature-controlled room, using more sensitive temperature measuring equipment. In this manuscript we will analyse all experiments from our lab performed in the last five years covering hand temperature measurements during RHI induction together, including this last study in a temperature-controlled room, to investigate whether we can replicate the hand temperature drop shown by Moseley et al. (Moseley et al., 2008).

Methods

Experiments

Out of all experiments in our lab in the last five years, five recent experiments have been included in this study based on 3 criteria: 1) the traditional RHI was conducted (synchronous and asynchronous stroking), 2) in healthy participants, 3) temperature was measured before and after stroking on both the test hand and a control location. The included experiments and specifics are presented in Table 1. All participants were naive to the purpose of the various experiments and written informed consent was obtained from all individual participants prior to the experiments. These experiments were conducted in accordance with the standards of the local ethical committee and the declaration of Helsinki.

Table 1 | Overview of the experiments analysed in the current study.

Experiment (dataset)	Participants	Test and control location	Temperature measurements	Stroking speed	Trials per condition
1	30 participants All female Mean age 21.8 ± 2.4 years	Test hand: left Control: cheek	Laser thermometer Once before, once after stroking	± 15–30cm/s	2
2	63 participants 39 female Mean age 23.9 ± 4.4 years	Test hand: both (counterbalanced order, data for both hands collapsed in the current analysis) Control: other hand	Laser thermometer 5× before, 5× after stroking	± 15–30cm/s	2
3	21 participants 10 female Mean age 23.9 ± 4.4 years	Test hand: right Control: left hand	Laser thermometer Once after stroking	3cm/s 30cm/s	2
4	28 participants 14 female Mean age 32.0 ± 12.2 years	Test hand: right Control: left hand	Laser thermometer Once after stroking	0.3cm/s 3cm/s 30cm/s	2
5	25 participants 13 female Mean age 22.4 ± 2.0 years	Test hand: right Control: left hand	Button thermometer Continuously during experiment, every second, resolution 0.0625 Co. In a temperature-controlled room	± 15–30cm/s	1

Experiment 3 included conditions in which stroking was performed with a plastic mesh instead of the generally used soft brush, but these conditions were not included in this analysis. Experiment 4 included condition on the ventral side of the hand (palm of the hand) but these were not included for analysis. Experiment 5 included conditions in which the RHI was performed inside a MIRAGE setup (Newport et al., 2010; Newport, Preston, Pearce, & Holton, 2009), but these conditions were also not included in this study. The data on proprioceptive drift and questionnaire responses (but not temperature data) from Experiment 1 was previously published in (Keizer, Smeets, Postma, van Elburg, & Dijkerman, 2014) as a control group. The data on proprioceptive drift and questionnaire responses (but not temperature data) from Experiment 2 is published in (Smit, Kooistra, Van der Ham, & Dijkerman, 2017). The data from Experiment 3 and 4 was previously published in (Van Stralen et al., 2014).

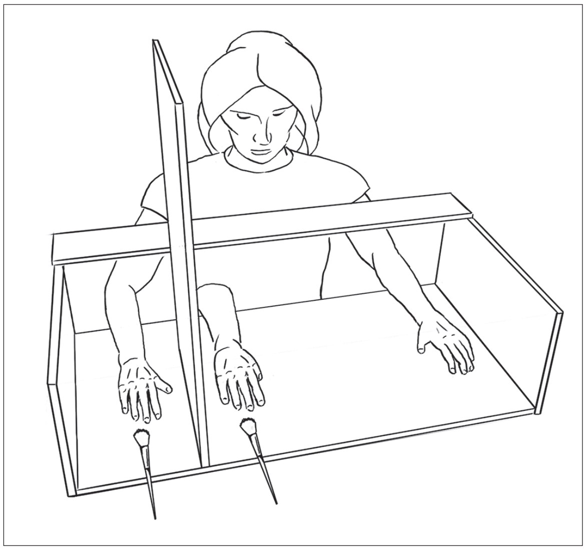

Figure 1 | Overview of the experimental setup. In Experiment 3, 4 and 5 and half of the trials in Experiment 2, the right hand was the test hand, as depicted here. In Experiment 1, as well as in half of the trials in Experiment 2, the left hand was the test hand. The large vertical screen is depicted hiding the test hand from view. It could also be placed horizontally on top of the setup, to hide all three hands from view.

Setup

Participants were seated with their forearms resting palms down on a table, within a wooden framework (75×50×25 cm). A rubber hand (including forearm) was placed in front of the participant, 17.5 (Experiment 1&2), 14 (Experiment 3&4) or 20 (Experiment 5) cm more to the body midline than the real hand it substituted (see Figure 1). A screen could be placed either vertically, occluding the real test hand from view during stroking but not the other hand or the rubber hand, or horizontally, occluding all three hands during proprioceptive drift recordings. The arms were covered from view by the wooden framework.

Tactile stimulation

Tactile stimulation (stroking) was delivered using a soft brush, to the dorsal side of the test hand and the rubber hand during 90 seconds. Stroking was always from knuckle to fingertip, and the stimulation of the real and the rubber hand was either synchronous (both spatially and temporally aligned) or asynchronous (difference between stroking on the real and on the rubber hand was unpredictable) (trials in counterbalanced order in all experiments). Stroking speed was unpredictable in Experiment 1,2 and 5 (around 20cm/s), while in Experiment 3 and 4, it was controlled at respectively 3cm/s and 30cm/s (Experiment 3) or 0,3cm/s, 3cm/s and 30cm/s (Experiment 4). Stroking speeds between 15 and 30cm/s are quite frequently used in the literature, although the exact stroking speed is most often unknown as stroking frequency is reported instead (some recent examples: (Dempsey-Jones & Kritikos, 2017; Grynberg & Pollatos, 2015; Lane, Yeh, Tseng, & Chang, 2017; Marotta et al., 2016; Suzuki, Garfinkel, Critchley, & Seth, 2013). Stroking speeds between 1 and 10cm/s would specifically target C-tactile fibres, and are considered more pleasant than slower and faster stroking (India Morrison et al., 2010; Olausson et al., 2010). Please see Van Stralen et al (Van Stralen et al., 2014) for a discussion on how this affects the RHI experience. Within this manuscript, we will group stroking speeds above the optimal C-tactile fibre range under “normal”.

Temperature recordings

In Experiments 1-4, temperature was recorded before and after stroking with a Raytek handheld Autopro (ST25) laser thermometer (resolution ± 0.2°C) on the dorsal side of the test hand, as well as on a control location (cheek in Experiment 1, the non-stimulated hand in Experiment 2-5). In Experiment 5, the temperature of the test hand, non-stimulated hand and the rubber hand (environment) was measured continuously with a frequency of 1 Hz and a resolution of 0.0625°C using iButton® temperature loggers (DS1922L) placed on the centre of the dorsal side of the hands. This experiment was conducted in a temperature-controlled room (19°C).

Procedure

At the start of a trial, all three hands were occluded from view by the wooden screen (horizontally placed). In Experiment 1-4, skin temperature was measured at the dorsal side of the test hand and on the control location. In Experiment 5, the computer time at the start of stroking was logged as skin temperature was measured continuously during the whole experiment. Furthermore, in all experiments, the perceived location of the test hand and the non-stimulated hand was recorded. The experimenter moved her index finger along the back of the setup where a ruler was attached out of view from the participant. The direction was counterbalanced. Participants reported verbally when they thought the experimenter's finger mirrored the perceived location of their own index finger. This was performed for both hands. Next, participants closed their eyes, and the wooden screen was put up vertically to reveal the rubber hand and non-stimulated hand. Stroking was then applied (synchronous or asynchronous) after which participants were asked to close their eyes again so that all hands could be occluded from view. Skin temperature and perceived location of both hands were obtained again. Then, the participant was asked to fill out the 'rubber hand illusion questionnaire' (M Botvinick & Cohen, 1998; Kammers, de Vignemont, et al., 2009). At this time, they removed their hands from the setup.

The rubber hand illusion questionnaire consisted of ten statements (Kammers, de Vignemont, et al., 2009) (see Supplementary material); the first three statements are illusion-related and the remaining seven are control statements. For Experiment 5, an additional statement was added, which was not analysed in the current study (statement 11; 'It felt as if my real hand was at the location of the rubber hand'), as pilot testing showed some participants considered the original 3 illusion-related statements did not describe their experience in the MIRAGE setup sufficiently (not included in this analysis). Participants were asked to indicate how much they agreed with each statement on a 10-point Likert scale ranging from 1 "I strongly disagree" to 10 "I strongly agree". In the current study, the first three (illusion-related) statements were analysed: "1) It seemed as if I was feeling the touch at the location where I saw the rubber hand being touched", "2) It seemed as though the touch I felt had caused the stimulation on the rubber hand" and "3) I felt as if the rubber hand was my own hand".

Additionally, three out of the five experiments tested how pleasant participants rated the stimuli. In Experiment 1, this was asked once, on a Likert scale of 1-10. In Experiment 3 and 4, pleasantness was rated after every trial, on a visual analogue scale that gave an output range between 1 and 5.

Data analysis

Outlier selection

Within each individual dataset (one from each experiment), outliers (>3SD from the mean) were excluded for each outcome measure as well as participants who failed to follow instructions (for instance moved their hands during proprioceptive drift measurements). In dataset 1, out of 30 participants, 1 was excluded for the analysis of hand temperature (>3 sd from average), 0 for the questionnaire and 2 for proprioceptive drift (>3 sd from average). In dataset 2, no participants were excluded for any of the analyses. In dataset 3, out of 21 participants, 1 was excluded for all analyses due to scores >3 sd from average. In dataset 4, out of 28 participants, 0 were excluded for the analysis of hand temperature: 1 for the questionnaire (failed to follow instructions) and 4 for proprioceptive drift (moved their hands or indicated something other than the felt location of the real hand). In dataset 5, out of 25 participants, 1 was excluded for all analyses (kept moving the hands), 1 was excluded for the analysis of hand temperature (>3 sd from average), 0 for the questionnaire and 1 for proprioceptive drift (moved the hands on several occasions before indicating the perceived location).

Subjective ratings and proprioceptive drift

To verify whether the rubber hand illusion was successfully induced in the included experiments, we analysed subjective strength of the illusion and proprioceptive drift separately in each dataset.

Results of the questionnaire responses in dataset 1 (Keizer et al., 2014), 2, (Smit, Kooistra, van der Ham, & Dijkerman, 2017) 3 and 4 (Van Stralen et al., 2014) were previously published and are discussed in depth in these papers. No participants were excluded that were not also excluded in the published papers. We performed Wilcoxon signed-rank tests per dataset per stroking speed to compare the average ratings on the test statements (1, 2 and 3) to a (usually deemed "neutral") score of 5. As the data did not resemble normal distributions, we performed non-parametric tests, similar to Keizer et al. (Keizer et al., 2014) and Smit et al. (Smit et al., 2017). Bayesian equivalents of these non-parametric tests are not yet commonly available.

We calculated proprioceptive drift by taking the difference between the perceived and the real location of the hand after stroking (averaged in case of 2 trials/condition), with a positive difference reflecting a drift in the direction of the rubber hand. Proprioceptive drift of the test hand was compared between synchronous and asynchronous stroking conditions per dataset per stroking speed using a paired samples comparison in JASP (Jasp Team, 2017; Morey & Rouder, 2015), which uses a Jeffrey's Bayesian t-test (Rouder, Morey, Verhagen, Swagman, & Wagenmakers, 2016). This procedure compares a model with an effect of Synchrony (with a Cauchy prior, scaled r=0.707, on effect size, so H+: $\delta \neq 0$,) with the Null model (H0, $\delta = 0$) (default uninformative priors in JASP). 2 participants from experiment 1 were excluded based on proprioceptive drift values >3sd from average, that were not excluded in Keizer et al. (Keizer et al., 2014) due to the nature of their non-parametric analysis and a slightly different calculation of proprioceptive drift.

Temperature analysis

For each participant in all experiments, we calculated the temperature difference at the test hand and the control location by subtracting the temperature after stroking from the temperature before stroking. If an experiment contained two trials per condition, these two temperature differences were averaged. Temperature differences were calculated for the test hand and on a control location in the synchronous and asynchronous condition. Only the temperature data from dataset 3 and 4 were previously published in Van Stralen et al. (Van Stralen et al., 2014). No participants were excluded that were not also excluded in Van Stralen et al. (Van Stralen et al., 2014).

First, to investigate the collective picture these studies give, we performed a conventional meta-analysis. For this, temperature differences in the four conditions (location (2) x synchrony (2)) were combined into one outcome measure: we controlled the difference in temperature change in the test hand and the control location in synchronous ("sync") condition for that in asynchronous ("async") condition. Thus, Tdc=(Tchange test hand sync - Tchange control location sync) – (Tchange test hand async – Tchange control location async) with Tchange=(temperature at end of stroking) – (temperature at start of stroking). A negative Tdc would imply a drop in temperature as a result of the RHI. For the meta-analysis we used a random effects model in OpenMetaAnalist. Within subject conditions in experiment 3 and 4 (stroking speed) were entered as separate studies.

Next, we used the BEST package in R: (Kruschke, 2013) to get a Bayesian posterior estimate for average hand temperature change in the test hand in RHI conditions minus control conditions. This package can handle informative priors. We investigated how much of the posterior distribution fell inside a region of practical equivalence (ROPE) (Kruschke, 2013). The model used was a *t*-distribution, with mean μ, standard deviation σ and degrees-of-freedom parameter df. For σ and df, we used broad priors as described by Kruschke (Kruschke, 2013) prior σ: gamma distribution with mode=sd(data) and sd=sd(data)*5, prior df: gamma distribution with mean=30 and sd=30). We used an informative prior for μ based on the results by Moseley et al. (Moseley et al., 2008) who reported an average temperature change difference in the test hand between RHI and control conditions of -0.27 degrees (SEM=0.11, n=11). We used the Bayesian MCMC process (3 chains) with an adaptive phase of 100 iterations, 1000 iterations burn-in and 33334 iterations sampling (default settings in the BEST package). Convergence was reached for all parameters (potential scale reduction factor was 1.00 for μ and σ, 1.01 for df).

Finally, we did a Bayesian correlation analysis in JASP (Jeffreys, 1961; Ly, Verhagen, & Wagenmakers, 2016; van Doorn, Ly, Marsman, & Wagenmakers, 2016; Wagenmakers et al., 2016) to see if temperature changes in the temperature change of the test hand (both in synchronous and asynchronous conditions) correlated with subjective strength of the illusion (average questionnaire ratings on question 1, 2 and 3) or proprioceptive drift of the test hand. We included both Synchrony conditions as some individuals in RHI experiments report some embodiment even in asynchronous conditions. As questionnaire ratings were not following a normal distribution, and temperature changes appeared to be more heavily tailed than a normal distribution, a rank correlation was performed. We also performed a rank correlation to investigate a possible relationship between pleasantness ratings and test hand temperature change. For the latter analysis, the pleasantness ratings of synchronous stroking in Experiment 3 and 4 were averaged and resized to 1-10 with the calculation (10-1)*(rating-1) / (5-1) +1). Additionally, we performed a Bayesian Pearson correlation to find out if there was a correlation between hand temperature at the start of an experiment and test hand temperature change.

Results

First, it was made sure that all studies involved had successfully elicited the RHI. Results of the questionnaire responses and proprioceptive drift in dataset 1 (Keizer et al., 2014), 2 (Smit et al., 2017), 3 and 4 (Van Stralen et al., 2014) were previously published. Please see these papers for a more elaborate discussion of these results.

Questionnaire ratings

Wilcoxon signed-rank tests showed that questionnaire ratings on the test statements in synchronous conditions were larger than neutral score of 5 in each dataset (dataset 1: median 7.08, $p<.001$, $r=0.51$; dataset 2: median 7.33, $p<.001$, $r=0.76$; dataset 3,slow: median 8.08, $p<.001$, $r=0.83$, normal: median 7.5, $p<.001$, $r=0.83$; dataset 4 , slowest: median 7.33, $p=.001$, $r=0.60$, slow: median 7.67, $p=.001$, $r=0.82$, normal: median 8.0, $p=.001$, $r=0.76$).

The median ratings on the test statements (1,2 and 3 combined) after synchronous stroking is depicted in Figure 2.

Proprioceptive drift

Average proprioceptive drift of the test hand was compared between synchronous and asynchronous conditions in each dataset. Bayes factors were in favour of the model that included an effect of Synchrony: i.e. proprioceptive drift was different in synchronous (sync) than in asynchronous (async) conditions, compared to a model without an effect of Synchrony. Estimated mean proprioceptive drift was larger with synchronous than with asynchronous stroking in all datasets. The estimated mean and standard deviation in cm, and BF are given in Figure 3.

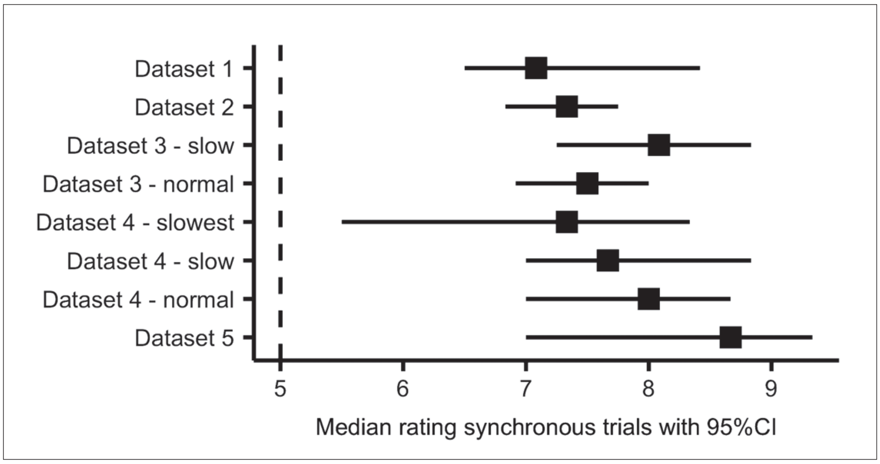

Figure 2 | Forest plot of group median questionnaire ratings on the test statements (rating of 1,2 and 3 averaged) in synchronous conditions. Horizontal lines depict a (bootstrapped, 10000 samples) 95% CI on the median. Note that all datasets show that ratings of the test statements were above a neutral score of 5.

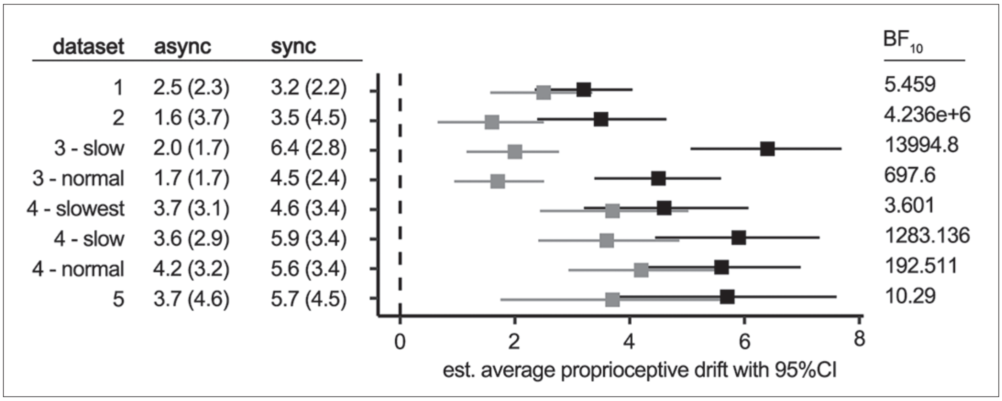

Figure 3 | Forest plot of estimated mean proprioceptive drift. Synchronous stroking is shown in black, asynchronous in gray. Horizontal lines depict a 95% CI on the mean. Note that all studies show proprioceptive drift of the test hand as a result of the RHI, although in the slowest stroking condition in dataset 4 this effect is less clear. In the table on the left, estimated mean and standard deviation per dataset is given, with on the right side of the graph the BF_{10}.

To summarise, the ratings of the test statements in the questionnaire and proprioceptive drift results suggest that all 5 studies successfully induced the rubber hand illusion.

Temperature: meta analysis

The main goal of the current study was to see if we find evidence in favour of a hand temperature change related to the RHI. First, we performed a conventional meta analysis of our five experiments. For this analysis, temperature differences in the four conditions (Location (2) × synchrony (2)) were combined into one output measure (Tdc, see methods section). This is the output measure used in Van Stralen et al. (Van Stralen et al., 2014), which covered dataset 3 and 4 and reported a RHI related temperature drop in the test hand. A negative Tdc would imply a drop in temperature as a result of the RHI. However, the meta analysis showed no significant effect of RHI on hand temperature, the estimated tdc was -0.06 (95% CI -0.17, 0.06, p=.337) (see Figure 4).

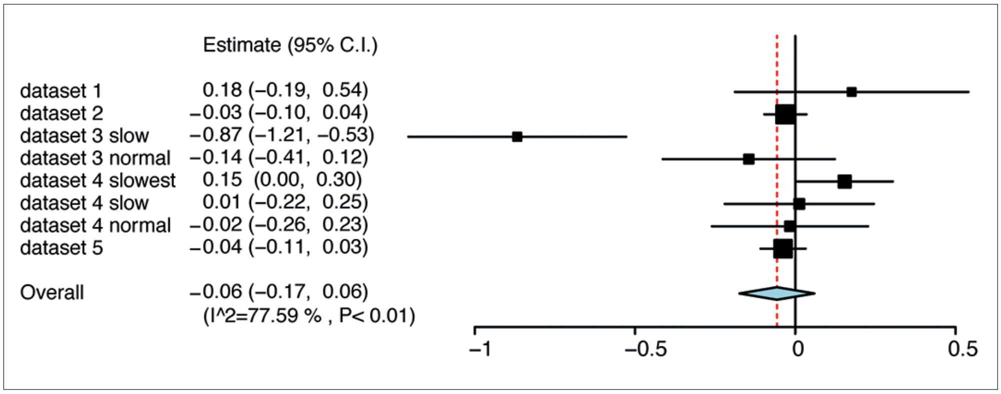

Figure 4 | Forest plot of average Tdc in the different Experiments and Stroking Speed conditions. The Tdc represents the change in temperature of the test hand in synchronous versus asynchronous conditions, relative to the same temperature change in the control location. A negative Tdc would imply a drop in temperature as a result of the RHI. The diamond shape depicts the weighted average (including dataset 3), which is not significantly different from zero.

The forest plot illustrates that the reported cooling of the hand in the RHI in Experiment 3 is rather eccentric (even compared to the original Moseley et al. (2008), who reported a Tdc of -0.27) and it could not be replicated using the same methods (Experiment 4). Heterogeneity in the meta analysis was significant with a I^2 of 77.6% (tau^2=0.017, p<.001), which indicates substantial heterogeneity, i.e. the studies are not all evaluating the same effect. This seems to be caused by the results from the slow stroking condition in experiment 3 (3cm/s), as I^2 drops to 20.1% (tau^2=0.001, p=.276) when excluding this data subset (but not that of the slow stroking condition in experiment 4). A subgroup meta analysis with stroking speed as the covariate (continuous random effects) shows a Tdc estimates of -0.033 (95% CI -0.080, 0.013) for normal stroking speeds, -0.418 (95% CI -1.281, 0.444) for slow stroking speed and 0.158 (95% CI 0.004, 0.304) for the slowest stroking speed. None of these subgroups show a significant RHI related hand temperature drop (normal: p=.155, slow: p=.342, slowest: NA as there is only one dataset with this stroking speed). When excluding the slow stroking condition in experiment 3, the estimated tdc was -0.01 (95% CI -0.06, 0.05; p=.774).

The slow stroking condition in experiment 3 seems to have generated very different results from the identical experimental condition in experiment 4. To test this, we ran an additional Bayesian unpaired comparison between the slow stroking condition in dataset 3 and 4 (see Gronau et al., 2017) using JASP. The Bayes factor of BF_{10}=217.8 shows that the data were far more likely to have occurred under the alternative (dataset 3≠dataset 4) than under the null hypothesis. Based on this finding and the heterogeneity analysis, we will report further analyses both including and excluding the data from the slow stroking condition in experiment 3.

Dissimilarity of dataset 3

We were interested to see what caused the dissimilar Tdc in dataset 3. It has been suggested that RHI is larger when your hands are colder (Kammers et al., 2011). Room temperature in experiment 3 was slightly lower (on average 18.4 ^{o}C) than in experiment 1 (20.3^{o}C), 4 (22.4^{o}C) and 5 (20.8^{o}C) (no data on room temperature in experiment 2 is available). Therefore, we checked whether hand temperature at the start of a condition correlated with temperature change in that hand in that condition in all datasets (collapsed). There was moderate evidence against such correlations (test hand sync: Pearson's r=0.062, BF_{10}=0.128, async: r=0.165, BF_{10}=1.809; control sync: r=0.047, BF_{10}=0.107, async r=-0.045, BF_{10}=0.104). Also, hand temperature at the start of trials was not lower in experiment 3 than in the others (Bayesian independent samples *t*-test: sync trials: BF_{10}=0.188, async: BF_{10}=0.194).

Furthermore, based on the conclusions of Van Stralen et al (Van Stralen et al., 2014), temperature differences in the hands may relate to affective experience rather than changes in embodiment. Three out of the five experiments tested how pleasant participants rated the stimuli. However, when excluding dataset 3, slow condition, there was moderate evidence against a correlation between pleasantness ratings and temperature change of the test hand (Kendall's tau=-0.029, BF_{10}=0.138). (When including dataset 3, slow condition, the Bayes factor is indecisive: Kendall's tau=-0.156, BF_{10}=0.912.)

We have found no direct explanation for the dissimilar results in experiment 3 in our data. We will speculate on further possible differences between experiment 3 and 4 that may have caused the temperature changes in experiment 3 in the discussion section.

Evidence for the null effect

The conventional meta-analysis did not find a significant RHI related temperature change. To investigate the strength of this null effect, we directly examined how much evidence we find that for the idea that the RHI results in a meaningful temperature drop in the test hand. Bayesian statistics offers the possibility to include previous beliefs. As Moseley et al. (Moseley et al., 2008) give mean and variance information on the temperature drop in the hands, we could include this as an informative prior. We investigated what percentage of the posterior distribution of temperature change in the test hand in synchronous minus asynchronous conditions, falls inside a region of practical equivalence (ROPE) to zero temperature change (Kruschke, 2013).

Figure 5A illustrated how the credible t-distributions described our data (excluding slow condition in dataset 3), as well as the difference with the data from Moseley et al. (Moseley et al., 2008). As can be seen in Figure 5B, the estimated mean RHI related temperature change in the test hand (μ in the model) was 0.00383°C, and the 95% HDI is from -0.0504 to 0.0579. Estimation for σ was 0.33521 (HDI 0.2717 to 0.3996) (which is similar to the standard deviation in the data from Moseley et al., 0.11* √11=0.3648287) and df 3.95845 (HDI 1.9267 to 6.5541). Using a ROPE of [-0.1 : 0.1°C], 100% of the posterior distribution fell within the ROPE, i.e. was equivalent to zero (see Figure 5B). Given the resolution of the measuring equipment used in all but 1 of the studies (±0.2°C) we consider this a reasonable ROPE, but we plotted dependence of how much of the posterior falls inside the ROPE as a function of the width of the ROPE in figure 5C so readers can consider their own thresholds. When including the slow condition in dataset 3, results are similar. Estimated μ: -0.0348°C, (HDI -0.0914 to 0.0223), σ: 0.3560 (HDI 0.2941 to 0.4225) and df: 2.9598 (HDI 1.7640 to 4.3793), 99% within a -0.1: 0.1°C ROPE.

Correlation analyses

Finally, we checked whether over all conditions, temperature change of the test hand (both in synchronous and asynchronous conditions) correlated with subjective strength of the illusion (average questionnaire ratings on question 1, 2 and 3), including both synchronous and asynchronous stroking. The BF_{10} that quantifies evidence in favour of a two-sided alternative hypothesis that the population correlation does not equal 0, was 0.207 (Kendall's tau=-0.051), which suggests moderate evidence in favour of the Null model (similar when including dataset

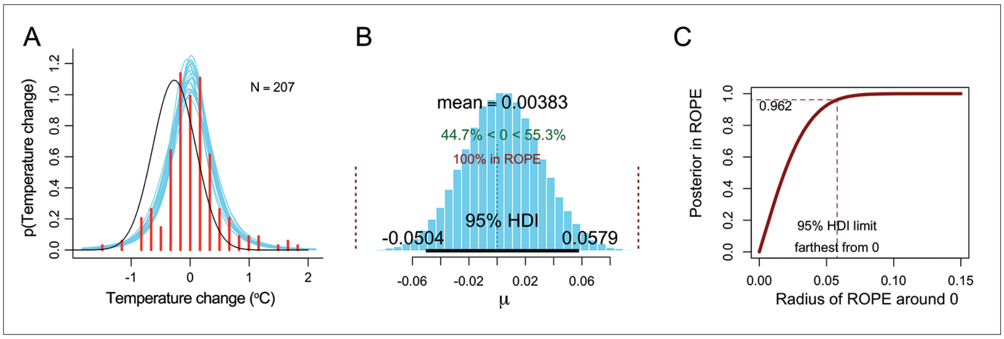

Figure 5 | Results from the ROPE procedure with an informative prior based on the data from (Moseley et al., 2008) panel A shows in red (medium gray when printing grayscale) a histogram of our data on the temperature change in the test hand in RHI trials minus control trials, with 20 credible *t*-distributions in blue (lightest gray). Superimposed in black is the prior distribution we used (normal distribution, mean=-0.27, sd=0.11* √11). Panel B shows the posterior probability distribution for μ in blue, with HDI credible interval in black, percentage of the distribution above and below zero in green and ROPE in red (dotted red lines represent the ROPE boundaries). Note that 100% of the posterior distribution fell within the ROPE, i.e. was equivalent to zero. Panel C shows the relation between the choice of ROPE radius and fraction of the posterior that falls within the ROPE.

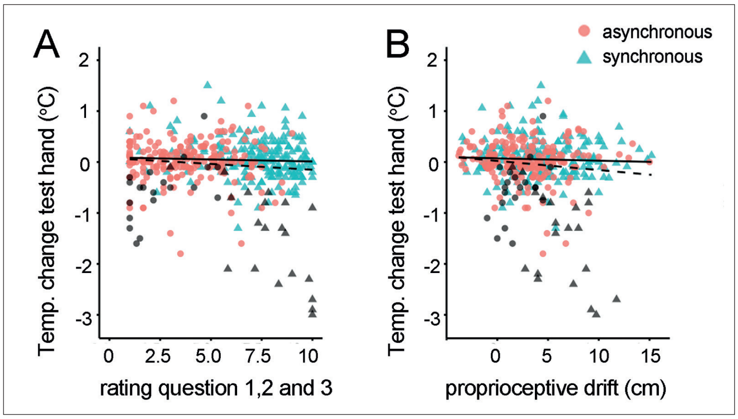

Figure 6 | Scatterplots of the correlation analyses. A): subjective strength of the RHI (average ratings on questionnaire items 1,2 and 3) vs temperature change during stroking in the test hand (no correlation, BF_{10}=0.207) B): proprioceptive drift of the test hand vs temperature change during stroking in the test hand (no correlation, BF_{10}=0.107). Solid regression lines represent the model when excluding dataset 3 - slow condition, dotted lines when including it. For dataset 3, slow stroking, asynchronous stroking conditions are depicted by gray circles, synchronous stroking conditions by gray triangles (darkest gray when printing grayscale). For the other data points, asynchronous stroking conditions are depicted by red circles (lightest gray), synchronous stroking conditions by blue triangles (medium gray).

3-slow: Kendall's tau=-0.048, BF_{10}=0.197). Similarly, there was moderate evidence against a correlation between proprioceptive drift of the test hand and temperature change of the test hand (Kendall's tau=-0.033, BF_{10}=0.107, similar when including dataset 3-slow: Kendall's tau=-0.050, BF_{10}=0.207) (see Figure 6).

Discussion

The current study investigated whether temperature changes are a reliable measure of body (dis)ownership, as suggested in several studies (Hohwy & Paton, 2010b; Kammers, Rose, & Haggard, 2011b; Moseley et al., 2008; Tsakiris et al., 2011) but disputed in several others (David et al., 2014; Grynberg & Pollatos, 2015; Paton et al., 2012; Rohde et al., 2013; Thakkar et al., 2011). We conducted an analyses of data collected during five experiments from our lab (with a total of 167 participants) that used the Rubber Hand Illusion (RHI) and measured hand temperature, to see whether we find evidence in favour of a hand temperature change as a result of the RHI. All experiments in the analysis replicated the subjective experience of body ownership over the fake hand, as well as proprioceptive drift of the test hand associated with the RHI. We found that a conventional (frequentist) meta-analysis of our results did not show a significant RHI related change in hand temperature. Moreover, Bayesian ROPE analysis showed that over all experiments, when correcting temperature change in the test hand with synchronous stroking for temperature change with asynchronous stroking, the estimated mean temperature change is equivalent to zero (100% within our defined ROPE), even though we included the results by Moseley et al. (2008) as an informative prior. Finally, a Bayesian correlation analysis showed that temperature differences did not correlate with subjective strength of the RHI or with proprioceptive drift. Concluding, based on our conducted experiments there is evidence against a RHI-dependent change in hand temperature. This suggests that a drop in temperature of the hand is not a reliable measure of hand (dis)ownership.

The current study therefore finds evidence that the temperature drop described in previous studies (e.g. (Moseley et al., 2008) cannot be replicated. This is in line with other studies that show difficulty in replicating hand temperature change as an index of the RHI. Some studies showed an illusion-related hand temperature drop (Kammers, Rose, Haggard, et al., 2011; Moseley et al., 2008; Tsakiris et al., 2011) while others did not (David et al., 2014; Grynberg & Pollatos, 2015; Paton et al., 2012; Thakkar et al., 2011; van Stralen et al., 2013) or temperature change was present independent of stroking synchrony (Rohde et al., 2013). The inconsistency in replicating a temperature drop as a proxy of the RHI may suggest that other factors apart from the effect of the illusion influenced temperature of the skin. First, there is the hypothesis that stroking speed is an influential factor of temperature changes of the skin. This idea arises from literature on affective, pleasant touch. Pleasant touch is associated with the processing of signals from C-tactile fibers, situated in the hairy skin. C-tactile fibers have been shown to respond to stroking with a velocity between 1–10cm/s and project to the posterior insula cortex (Olausson et al., 2010). Studies have shown that the processing of pleasant touch is tightly connected to the processing of bodily state such as temperature of the body (Rolls, 2010). For example, a skin-temperature of 32°C results in the strongest feeling of pleasantness of stroking compared to lower or higher skin-temperatures (Ackerley et al., 2014). Therefore, the tight link between pleasantness and temperature might assume that temperature drop during the RHI may be more pronounced during slow stroking conditions. However, we do not find any evidence that slow stroking has a unique effect on temperature drop. First, the slow stroking conditions do not show a significant higher temperature drop compared to higher stroking velocities. Although slow stroking in experiment 3 resulted in a temperature drop (but not in experiment 4), we showed that dataset 3 is deviant for reasons other than that of the effect of affective touch. Moreover, in the original experiment of (Moseley et al., 2008), there was no specific stroking speed nor subjective ratings of pleasantness described. In the known replications of the RHI-related hand temperature drop, stroking speed was not particularly low (Kammers, Rose, Haggard, et al., 2011; Tsakiris et al., 2011) see also (Rohde et al., 2013). Stroking frequencies of 1 Hz are reported, which would suggest stroking speeds between 15 and 30cm/s. Replications with other bodily illusions and RHI variations use varying methods. Salomon et al. (Salomon et al., 2013) used a rather low stroking speed of 8cm/s in the full body illusions, but Hohwy and Paton (Hohwy & Paton, 2010a) used tapping as tactile input instead of stroking and Macauda et al. (Macauda et al., 2015) used vestibular input instead of tactile. Overall, this suggests that stroking speed and pleasantness were unlikely to be responsible for the temperature drop. Second, we do not find a significant correlation between pleasantness of the stroking and temperature drop. That is, stroking that is regarded as more pleasant did not result in a stronger decrease of hand temperature. Therefore, these results suggest that the experience of pleasantness of stroking does not influence temperature of the hand during the RHI.

Some other factors can be proposed. First, environmental temperature fluctuations may increase variation of body temperature during the experiment and thereby masking possible effects of the RHI. However, one of the experiments conducted in our lab (Experiment 5) was conducted in a temperature controlled room and still did not detect temperature changes of the hand as a result of the illusion, suggesting that environmental factors are not the primary cause of not detecting temperature drops. Additionally, if power problems were the reason that a RHI-related temperature drop in the hand is not consistently replicated, it would be expected that the current meta-analysis (N=167) showed a significant RHI-related temperature drop, which it did not. Nevertheless, room temperature in our experiment 3, which did show an effect of the RHI on hand temperature, was slightly lower than in the other experiments. This did not seem to moderate a RHI related hand temperature change by influencing the strength of the RHI through baseline hand temperature (see Kammers et al., 2011), as there was no correlation between hand temperature at the start of a trial and hand temperature change. Still, it may have caused direct changes in hand temperature change, for instance if participants moved less in certain conditions. Heat is an important by-product of muscle contraction. If participants are more inclined to keep their hands really still with synchronous stroking, for instance trying not to break this interesting illusion, their hands will get colder. This could cause a correlation between illusion strength and temperature changes in experiment 3 and possibly in other studies in the literature. While these temperature drops will be related to experimental condition, they are not directly related to feelings of body (dis-) ownership. This temperature change due to lack of movement would be larger in a colder room because the temperature difference between the hand and the room would be larger and the hand would cool down quicker. Furthermore, experimenters may show a bias in how they decide which trials to exclude or how to approach a participant in different conditions. For instance, being unconsciously inclined to be stricter about a participant keeping their hands motionless during a trial when it is a synchronous stroking trial could result in a relative lower temperature post-stroking of the hands in the synchronous condition as moving the hands will increase the hand temperature.

Another possible influence could be the duration of stroking. Moseley et al. (Moseley et al., 2008) used a rather long stroking duration of 7–8 minutes, while we used 1.5 minutes. Visual inspection of their Figure 1 indicates that the long stroking duration in (Moseley et al., 2008) may have increased hand temperature changes as a result of the RHI procedure, as it shows that hand temperatures kept decreasing for a few minutes. However, subjective experience of the illusion preceded temperature changes. It has been reported that for most participants, illusionary ownership over a rubber hand close to the real hand starts within 5-15 seconds (HH Henrik Ehrsson et al., 2004; Donna M Lloyd, 2007). A stroking duration of 1-2 minutes is therefore quite commonly used in RHI experiments (for example (Abdulkarim & Ehrsson, 2016; David et al., 2014; Hegedüs et al., 2014; Kammers, Verhagen, et al., 2009; Kammers, de Vignemont, et al., 2009; Kilteni, Normand, Sanchez-Vives, & Slater, 2012; Donna M Lloyd, 2007; Mohan et al., 2012; Preston, 2013; Rohde, Luca, et al., 2011) and Rohde et al (Rohde et al., 2013) did not replicate an illusion related drop in hand temperature using a 7 minutes stroking period. Moreover, studies that did replicate the drop in hand (or body) temperature did not use particularly long stroking durations (90 s. in (Kammers, Rose, Haggard, et al., 2011); 120 s in (Tsakiris et al., 2011). Therefore, together these studies indicate that the shorter duration of stroking in the current study is unlikely to be a cause for the lack of observed skin temperature changes.

A third factor that may influence temperature outcome are the characteristics of the experimenter. In one of our studies, two experiments were conducted in an identical set-up, apart from the person that conducted the experiment (Van Stralen et al., 2014). In the first experiment (here Experiment 3), a clear temperature drop was found whereas in the second experiment (Experiment 4), which was conducted by another experimenter, this was not replicated. While this could be a coincidence, the influence of the experimenter on the experience of touch has been investigated by studies on social touch. There is evidence that neural activation varies depending on what the source of tactile stimulation is (Alberto Gallace & Spence, 2010). In a study of Gazzola et al. (Gazzola et al., 2012), heterosexual male participants were made to believe to be caressed by either a man or a woman, although the stroking was in fact always delivered by a female. The perceived sex of the experiment leader changed the affective valence of the touch, and even more, it changed activation within the primary somatosensory cortex. Another study investigated ingroup-outgroup differences in visual remapping of touch (VRT), an effect in which the observation of touch on another's body leads to greater sensitivity to tactile stimulation on one's own body. Results showed that detecting touch was most enhanced when viewing a touched face of a person that is regarded as a member of the same group compared to the observation of touch of an outgroup member (Serino, Giovagnoli, & Làdavas, 2009). These studies suggest that the impression of the person that applies tactile stimulation influences tactile processing. Although it might be suggested that an altered tactile processing leads to a different effect on the rubber hand illusion, studies on this topic are scarce. It has been reported that a higher degree of empathy (as a characteristic of the participant) increases the strength of the RHI (Asai, Mao, Sugimori, & Tanno, 2011). A recent publication (Rohde et al., 2013) examined whether manual stroking applied by an experiment leader affected the RHI compared to automated stroking by a device, without a person present in the experimental room. Results show no effect on vividness of the RHI between automated and manual stroking. Interestingly, as discussed in the introduction, a drop in temperature of the hand was only objectified in the manual stroking condition, and not with the automated stroking by a device. This temperature drop was independent of the synchronicity of stroking or the subjective experience of the RHI, i.e. the temperature drop was present in the experimental as well as the control condition. The authors offer several potential factors that explain the results, including the difference in characteristics of the stroking (force, irregularity or predictability of tactile and visual input) and the characteristics of the experiment leader (unconscious bias in how they perform the stroking in synchronous and asynchronous condition, arousal differences). Our results seem to support their finding that it might matter who -or what- is applying the tactile input. This underscores the great complexity of social touch, in which the exact role of skin temperature remains unclear.

In all, although the presence of temperature changes of the hands in RHI experiments might be determined by various factors, an overall analysis of RHI experiments in our lab in the last 5 years, covering five replications of the traditional RHI experiment and totalling 167 participants, shows evidence against a reliable cooling related to the RHI. In line with Rohde et al. (Rohde et al., 2013) our analysis therefore suggests that hand temperature changes in the RHI are not causally related to changes in body ownership.

Acknowledgments

We would like to thank Marlies de Bruijn for her help with data acquisition.

Chapter 9

Discussion

Touch is one of the most important and most underestimated senses in everyday life. Touch is provided through the (skin of our) body, but it also provides information *on* the body. That is, we are generally quite precise in distinguishing between parts of our own body and objects in the external world. And moreover, we feel that we *own* our body. Disturbances after lesions to the central nervous system may lead to impairments in body ownership. This thesis aimed to investigate the causes and modulating effects of disturbances in body ownership from a neuropsychological perspective. To discuss the results and implications in a systematic manner, the current chapter is divided in three sections.

9.1 Impairment in the perception of touch and body ownership; taking a perspective
Summary of findings
Theoretical integration and interpretation
Clinical implications and recommendations for future research

9.2 Cognitive mechanisms underlying impairments in body ownership impairments
Summary of findings
Theoretical integration and interpretation
Clinical implications and recommendations for future research

9.3 Modulation and treatment of impairments in the perception of touch and body ownership
Summary of findings
Theoretical integration and interpretation
Clinical implications and recommendations for future research

9.1 Impairment in the perception of touch and body ownership; taking a perspective

Summary of findings

The wide range of impairments in touch and bodily experience as a result of damage to the central nervous system, is described in **Chapter 2**. These disorders occur at multiple levels, ranging from primary somatosensory perception disorders (for example, a deficit in two-point discrimination or pressure sensitivity) to higher order disorders. The higher order aspects, also regarded as cognitive aspects, are how we interpret somatosensory information. This requires integration of different somatosensory signals with other sensory modalities (vision, hearing) and other cognitive functions such as memory and attention. The somatosensory system also generates information about our body; for example, knowing that the hand you see on your lap is yours. One of the disorders related to the perception of your body, is an impairment in the sense of body ownership. Multiple types of this impairment have been described, in which a denial or even rejection of ownership over (a part of the) body is regarded as a key symptom. These disorders can be present in the absence of other deficits, although it is more common that they influence, and are influenced by other tactile and cognitive deficiencies. The thought prevails that only a small percentage of patients develop a disbelief of awareness over (a part of the) body after stroke although the prevalence is still unknown (Vallar & Ronchi, 2009).

In **Chapter 8** we assessed 47 patients who suffered from a first-ever stroke. The patients underwent a neuropsychological examination that included tests targeting the entire somatosensory domain, and performed a test of the ability to discriminate left from right. A substantial part of the patients also underwent brain imaging and were entered into voxel-based lesion symptom mapping (VLSM) analyses. First, in this group, six patients (12.8%) reported suffering from a diminished sense of ownership over one of their limbs in the subacute phase, suggesting that body ownership impairments are not as rare as previously suggested. This is in line with another recent report that observed 7 out of 31 right hemispheric stroke patients showed body ownership impairments (Martinaud, Besharati, Jenkinson, & Fotopoulou, 2017). Second, our results also showed that the higher order aspects of the somatosensory system are involved in left right orientation (LRO). That is, impairments in structural body representation deficits (as measured by finger gnosis) as well as subjective body ownership deficits (as measured by subjective reports) predicted impairments in LRO. This was most profound when stimuli had to be rotated in order to discriminate left from right, as the prediction was strongest for stimuli viewed from a third-person perspective. Lastly, VLSM analyses showed a significant association between LRO deficits and lesions in the right insular cortex. The insular cortex has been associated with interoceptive awareness

(Craig, 2002, 2009) and the sense of body ownership (Karnath, 2005; Tsakiris et al., 2007a). In conclusion, our study suggests that perspective taking and body representation are tightly connected, and that the right insula seems to be an important area to mediate these functions.

Theoretical integration and interpretation

Our results suggest that impairment in the higher order aspects of the somatosensory system are involved in LRO. The VLSM analysis in this thesis showed that the insula is also associated with LRO tests in which taking another persons' perspective was required. In addition, impairment in LRO was significantly associated with body representation deficits, including structural body representation (finger agnosia) and body ownership problems. That is, impairments in finger gnosis as well as subjective body ownership deficits predicted LRO but only for stimuli in which a third person perspective had to be taken. A possible explanation would be that taking a third person perspective demands motor- and visual imagery (Brady et al., 2011; Choisdealbha et al., 2011; Conson et al., 2012)) and this may be hindered by problems in recognizing or feeling your hand as your own. A recent study on patients suffering from body awareness problems (anosognosia for hemiplegia) after stroke showed that these patients exhibited more deficits in mentally taking the third person perspective (Besharati et al., 2016). Other studies demonstrated that patients show clear improvements in bodily awareness when they are provided with visual feedback of their own body in the third person perspective, i.e. when visual feedback of their paralysis is provided via mirrors or video replays (Besharati et al., 2014, 2016; Fotopoulou et al., 2011; Jenkinson et al., 2013). Similarly, making verbal judgements from a third person perspective increases bodily awareness (Marcel, Tegnér, & Nimmo-Smith, 2004). Previous research has postulated that the insular cortex is in particular involved in integrating bodily interoceptive signals related to an egocentric representation (Tsakiris et al., 2007a; Vogeley & Fink, 2003). Our study in this thesis suggests that the insula mediates spatial aspects of bodily perception as well, and may be involved in mapping a third person perspective to a first person perspective. In conclusion, we show that there is a wide range of impairments of the somatosensory system that can arise after stroke, ranging from primary to higher order aspects. The higher order impairments (fingergnosis and body ownership) are associated with impairment in LRO difficulties after stroke.

Clinical implications and recommendations for future research

It is a common view that body ownership impairments are clinically infrequent and recover over time. Although a substantial proportion of our sample indeed showed recovery after stroke, body ownership impairments can be a chronic condition for some patients. Interestingly, our results also showed that body ownership impairments are not as infrequent as previously suggested. These data support our finding that the insular cortex is not only involved in body awareness, but also with structural and spatial representation of the body. Recent studies have suggested that the vestibular system is involved in anchoring the self to the body (Ferrè & Haggard, 2016; Ferrè, Lopez, & Haggard, 2014) in which signals from the external world are mapped to the bodily self. Moreover, the association between body ownership impairments and LRO suggests that bodily awareness is important for other cognitive functions, such as spatial perception. Although the exact locations and functions of vestibular cortical areas are still a matter of debate, there is consensus that the insular cortex plays a central role (Lopez, 2016b; Lopez & Blanke, 2011). Stimulation of this insular-vestibular network may reduce symptoms of visuospatial neglect and somatoparaphrenia (Bisiach et al., 1991; Rode et al., 1992; Salvato et al., 2016). Future studies could further explore the relation between spatial mapping of the bodily self, and it's association with the insular cortex. Promising candidates for future research include interventions using caloric vestibular stimulation (CVS) or galvanic vestibular stimulation (GVS), a technique in which the vestibular nerve is stimulated through transcutaneous electrical current.

9.2 Cognitive mechanisms underlying impairments in bodily experience

Summary of findings

Experimental studies to objectify the sense of body ownership are scarce due to a wide range of comorbid (sensory and cognitive) impairments. Therefore, most literature is based on anecdotal case descriptions, with limited knowledge on the cognitive factors underlying body disownership. In **Chapters 3 and 4**, we were able to systematically examine two patients who both showed impairments in body ownership after an acquired brain lesion. The patient in Chapter 3 suffered from an ischemic stroke, while the patient in Chapter 4 suffered from a tumour in the right parietal lobe. In both patients, we conducted the Rubber Hand Illusion (RHI), an experimental paradigm that allows a controlled manipulation of the experience of body-ownership (Matthew Botvinick & Cohen, 1998). These case studies show that both patients were highly susceptible to this illusion, compared to the unaffected hand (Chapter 3) and compared to healthy controls (Chapter 4). These results provide two insights in the phenomenon of body ownership impairments. First, patients with problems in the sense of ownership are more prone to accepting a foreign arm as their own. And second, both patients seem to rely strongly on visual input, rather than benefit from multisensory (tactile and visual) stimulation. That is, both patients showed a strong illusion during synchronous, multisensory stimulation, during visual input only (Chapter 4), and when multisensory stimulation was presented in asynchrony (Chapter 3). These results suggest that both patients did not benefit from multisensory integration. In fact, the patient described in Chapter 4 reported that only looking at a fake hand created the feeling "that this rubber hand is attached to my body, which

I don't experience with my real hand." The strong visual reliance was even better illustrated by the patient in Chapter 3, who showed a strong illusion by only looking at a fake hand. While stimulating the fake hand, she reported to experience as if she felt the 'seen touch' on her own hand, also known as vision-touch synaesthesia (in which a visual perception of touch elicits a conscious experience of touch).

Theoretical integration and interpretation

Our results suggest that problems in body ownership are caused by an erroneous integration of afferent somatosensory (tactile, proprioceptive) information with visual information. This is in line with studies that propose that the feeling of body ownership critically depends on multisensory integration (Matthew Botvinick & Cohen, 1998) and for review see (Maravita, Spence, & Driver, 2003), mediated by areas around the intraparietal sulcus and inferior parietal cortex, and the premotor cortex (Graziano, 1999; Graziano & Botvinick, 2002; Rizzolatti, Luppino, & Matelli, 1998). Indeed, although the exact lesion site of the case in Chapter 3 was unknown, the case described in Chapter 4 suffered from a lesion in the right parietal cortex. As a consequence of integration problems, the body representation of the case in Chapter 4 is largely built upon visual information, and easily distorted by afferent somatosensory information. There are a few other studies that found an increased subjective sense of ownership over a fake hand merely based on vision (Giummarra, Georgiou-Karistianis, Nicholls, Gibson, & Bradshaw, 2010; Pavani, Spence, & Driver, 2000; Tieri, Tidoni, Pavone, & Aglioti, 2015). In addition, when there is conflicting visual and proprioceptive information, visual information tend to override proprioception, which assumes that position sense is recalibrated based on visual information only (Holmes et al., 2006). A recent article on stroke patients with impairments in the bodily awareness showed that the majority of patients felt ownership over a rubber hand based on vision only, even when the rubber hand was moved by the experimenter (Martinaud et al., 2017). The strength of this so called 'visual capture' was positively associated with proprioceptive deficits, suggesting that when proprioceptive information is not available or informative, visual cues can generate recalibrated hand position as well as a feeling of hand ownership (Martinaud et al., 2017). Although it cannot be ruled out that proprioceptive sense was impaired in the (sub)acute phase after brain lesion, neither case in the current thesis suffered from proprioceptive impairments at the time of the experiment. This suggests that impairments in the proprioceptive sense are not a prerequisite to create a visual capture over the proprioceptive sense.

In conclusion, together these studies provide evidence that i) impairment in the sense of ownership can be examined by (an adjusted version of) the RHI, and ii) patients with impairment in the sense of ownership are more susceptible to inclusion of a rubber hand into their body representation, (possibly because of a strong reliance on visual information).

Clinical implications and recommendations for future research

The presence of body ownership impairments in clinical care is currently based on observations and subjective reports of a patient. A lack of insight in their impairments, a common comorbid symptom of body ownership problems, may lead to under diagnosis. This may lead to clinically hazardous situations; patients may falsely believe that they are able to stand up out of bed, or they forget to pay attention to the space around their affected arm. The results of the current studies contribute to a better understanding of the cognitive mechanisms underlying body ownership impairments, which may lead to improvement of the diagnostic process. However, our results showed that while patients with body ownership problems have some shared characteristics, there are many differences too. For example, the feeling as if your limb does not belong to yourself often concerns the right side, and in the majority of the cases it concerns specifically the upper limb. But, body disownership may also concern the complete left side of the body, or even the entire body. In some, but not all cases, patients suffered from visuospatial neglect. On the same account, sensorimotor deficits were present in most cases, but again, this is was not the case for each patient. A lack of insight in their deficit (anosognosia) is often reported, but again, not always a comorbid symptom. In some patients, symptoms are reduced by taking a third person perspective, but not in each patient (Marcel et al., 2004). These findings characterize the body ownership impairments and suggest that multiple combinations of causes can lead to problems in self-awareness. There might not be a unified theory that explains the different body ownership problems, but rather different combinations of factors that result in problems in body ownership. Individual experimental paradigms may be the first step to diagnose body ownership problems in terms of underlying sensorimotor and cognitive deficits, rather than a description of the phenomenology. This also means that certain treatment paradigms may be helpful for some patients, but not or to a lesser extent for others.

9.3 Modulation of impairments in the perception of touch and bodily experience

Summary of findings

In **Chapter 5**, we reviewed literature on the effects of self-touch on impairments in somatosensory function. Studies have shown that self-touch improves tactile detection in patients with primary tactile deficits. A small number of studies concerned with the effect of self-touch on bodily experience in healthy individuals have demonstrated that self-touch influences the structural representation of one's own body (Schütz-Bosbach et al., 2009; White et al., 2010). In Chapter 5, we demonstrated that an experiment comparable to the 'somatic RHI' was feasible to conduct in a heavily affected patient with a haemorrhagic stroke who was recovering from somatoparaphrenia, a delusion that a part of one's own body belongs to someone else. Moreover, we found that self-touch and implied self-touch modulated the sense of ownership and changed the affect towards the affected limb. That is, she developed more positive feelings towards the limb following self-touch. This was in line with observations we made days prior to the experiment, in which the patient showed an increase in affective caressing on her affected arm, and reported that it helped to reinstate her body representation. Interestingly, the case described in Chapter 4 also showed a different response to the RHI when the touch was more affective (pleasant), compared to touch that was regarded as less pleasant. Although this concerned passive touch and not self-touch, it suggests that the affective component of touch may have a unique contribution in regaining body ownership. Touch that is regarded as pleasant facilitates bonding and interpersonal communication, such as expressing your love by a sensual caress, or soothingly stroking a child's head. Pleasant touch involves a system that is anatomically and functionally distinct from the pathway for discriminative touch (Gordon et al., 2011; McGlone et al., 2007; Morrison et al., 2010; Olausson et al., 2002). Touch that is light, soft and has a stroking velocity ranging between 1-10cm/s is regarded as most pleasant, and is conveyed by slow-conducting, unmyelinated low threshold mechano-receptive fibers (C tactile fibers) that project to the posterior insular cortex (Gordon et al., 2011; McGlone et al., 2007; Morrison et al., 2010; Olausson et al., 2002) as well as by the regular large myelinated fibers projecting to the primary somatosensory cortex. In **Chapter 6**, we investigated whether affective, pleasant touch would have an effect on body ownership compared with regular touch in healthy participants. We indeed showed that pleasant touch had a stronger effect on the RHI than regular touch, in terms of proprioceptive drift. That is, touch that was regarded as most pleasant made participants more susceptible to accepting a foreign hand as their own. In addition, we investigated the temperature of the hand after the RHI. A drop in temperature of the hand as a proxy of the RHI has been postulated by Moseley et al (Moseley et al., 2008) and has been associated with disownership of the own hand. Our results showed that the temperature of the hand of healthy controls decreased in one experiment, but not in a second. In **Chapter 7**, we analyzed all data collected by our lab on the influence of the RHI on temperature of the hand and found again no consistent evidence for cooling of the hand after the induction of the RHI, in line with inconsistency across the literature. This suggests that a temperature drop is not a reliable outcome measure of the RHI. In conclusion, pleasant touch seems to consistently affect the proprioceptive drift, but not the subjective experience, or the temperature of the hand.

Theoretical integration and interpretation

Our finding that pleasant touch influences body representation provides a connection between processes involved in emotional labeling of somatosensation on the one hand, and body ownership on the other hand. These results build upon previous research that has shown an effect of touch on bodily functions and bodily development. For instance, a caress by a spouse can reduce heart rate, blood pressure and hormone secretion (Ditzen et al., 2007; Grewen et al., 2003) and touch given to low birth weight infants improves visual-motor skills (Weiss et al., 2004) and increases amplitude of cortical responses to light touch in premature infants (Maitre et al., 2017).

Based on our results it may however be concluded that the pleasant component of touch (that activates c-tactile fibres) in particular, modulates the body representation beyond that of regular touch. This finding sheds new light on the existing theories on the functional relevance of the c-tactile system. The c-tactile system is thought to have social and affiliative functions. The studies in the current thesis add to the existing knowledge that affective touch modulates the sense of ownership. That is, pleasant touch influences the sense of body ownership. Interestingly, touch that is applied on skin sites without c-tactile fibers (such as the palm of the hand) resulted in a less pleasant feeling and a less strong RHI compared to touch applied on skin that contains c tactile fibers. In addition, we showed in 2 patients with body ownership deficits that they responded differently to affective touch compared to regular touch. That is, affective touch seemed to enhance the feeling of ownership over their affected arm. An explanation for this finding may be that pleasant touch activates additional tactile input (i.e. by c-tactile fibers) that augments afferent information, which may subsequently lead to a boost of multisensory integration. The RHI, as well as the sense of body ownership, critically depends on multisensory integration (Botvinick & Cohen, 1998; Ehrsson, Spence, & Passingham, 2004; Maravita et al., 2003; Tsakiris & Haggard, 2005). Therefore, bottom-up input may be boosted by affective touch that increases multisensory integration, and thus heightens the sense of body ownership. Lloyd et al. (Lloyd, Gillis, Lewis, Farrell, & Morrison, 2013) also showed that pleasant touch enhanced the subjective experience of embodiment of the rubber hand (see also (Crucianelli et al., 2013)), however, in contrast to our findings, this effect was not different from the condition in which touch was applied to skin sites known to lack C tactile fibers (McGlone et al., 2012; Vallbo, Olausson, & Wessberg, 1999). This finding suggests that the experience of pleasantness contributes to body ownership as well, and not c-tactile fibers per se. C-tactile fibers in turn contribute to a pleasant experience, but other higher order processes such as the context in which the touch is administered may be involved in boosting ownership as well (Gentsch, Panagiotopoulou, & Fotopoulou, 2015; India Morrison, Bjornsdotter, & Olausson, 2011).

Clinical implications and recommendations for future research

Impairments in the bodily awareness after stroke are related to poor functional outcome (Prigatano, 2009). Rehabilitation methods however, have not been systematically investigated as yet. The current findings on affective touch may be a promising candidate for relieving symptoms of body ownership problems. It is, however, unclear whether affective touch is effective in patients with sensory loss. Interestingly, the case described in Chapter 5 suffered from sensory loss on the left side of her body, but she nevertheless kept caressing her affected arm frequently. This is in line with clinical observations of other affected patients; there seems to be a tendency to gently caress and stroke the affected arm, even when there is loss of sensory function. Interestingly, although patients report that the stroking is not perceived (at least not on the affected arm), results suggest that it actually leads to improvements in bodily awareness. Therefore, there is evidence that affective touch can help improve bodily awareness, even in patients with sensory loss. Future research should assess whether these treatment paradigms result in longer lasting effects and if this depends on the cognitive characteristics underlying body ownership impairment.

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Nederlandse Samenvatting

De tastwaarneming wordt gebruikt om te voelen wat er in je omgeving gebeurt, zoals het voelen van je sleutels in je rommelige tas of de warmte voelen van een hand op je schouder. De tastzin geeft ons niet alleen informatie over wat er buiten ons gebeurt, maar het geeft ons ook informatie over de staat, positie en vorm van ons lichaam. Dat is uniek aan dit zintuig, want het betekent dat het gedeelte waarmee we waarnemen, in dit het geval het lichaam, ook weer informatie geeft over datzelfde lichaam. Het zoeken naar een lichtknopje in het donker geeft mij dus niet alleen een idee over waar het lichtknopje zit, maar dit geeft mij direct ook informatie over de positie van mijn vingers en de lengte van mijn arm. Ook zijn we hierbij goed in staat om een onderscheid te maken tussen waar onze vingers eindigen, en waar het lichtknopje begint. Hoewel dit natuurlijk heel vanzelfsprekend klinkt, kunnen er bij sommige mensen problemen ontstaan in het lichaamsbewustzijn. Problemen in het lichaamsbewustzijn kunnen betekenen dat iemand niet meer overtuigd is van het feit dat een ledemaat van hem of haar is. Dit kan verschillende vormen aannemen.

In **hoofdstuk 2** worden de verschillende soorten stoornissen in de tast- en lichaamswaarneming beschreven die voor kunnen komen na hersenletsel. Stoornissen kunnen op verschillende niveaus voorkomen waarbij de primaire processen (zoals de detectie van een aanraking, pijn of temperatuur) verstoord kunnen raken. Ook hogere orde processen kunnen verstoord raken, zelfs wanneer de primaire processen onaangedaan zijn. Met ‘hogere orde’ worden processen bedoeld waarbij informatie uit andere zintuigen maar ook uit andere denkfuncties geïntegreerd en geïnterpreteerd worden. Er is dan een uitgebreider neuronaal netwerk betrokken. Zo kan een beroerte ervoor zorgen dat iemand niet meer in staat is om de vorm van een voorwerp te herkennen, terwijl diegene wel voelt *dat* er wat in de hand ligt. Dit betekent dat het primaire proces (detectie van een voorwerp) voldoende verloopt, maar dat het hogere orde proces (interpretatie) niet goed verloopt. Hogere orde stoornissen betreffen problemen in het herkennen en interpreteren van informatie om ons heen, of in het herkennen van informatie over ons eigen lichaam. Wanneer het ons eigen lichaam betreft, spreken we van stoornissen in de lichaamsrepresentatie. Lichaamsrepresentatiestoornissen bestaan uit i) structurele lichaamsrepresentatiestoornissen (kennis over de positie en vorm van lichaamsdelen) en ii) stoornissen in het lichaamsbewustzijn. In de klinische praktijk is de diagnostiek van lichaamsbewustzijnsstoornissen gebaseerd op observaties en subjectieve meldingen van een patiënt. Echter, een gebrek aan ziekte-inzicht is bij deze groep eerder regel dan uitzondering. waardoor een risico bestaat op onderdiagnose van lichaamsbewustzijnsstoornissen. Dit kan leiden tot gevaarlijke situaties; de patiënten kunnen ten onrechte geloven ze uit bed op kunnen staan, of vergeten aandacht te schenken aan de ruimte rondom het lichaam.

In **hoofdstuk 3 en 4** beschrijven we twee patiënten die lijden aan een stoornis in het lichaamsbewustzijn en trachten we te onderzoeken of de klachten van de patiënten objectiveerbaar gemaakt kunnen worden. Bijzonder aan deze beide patiënten is dat zij beiden weinig problemen hebben in de primaire tastwaarneming en motoriek. Ook is hun cognitief functioneren beperkt aangedaan, wat hen goed geschikt maakt om experimenteel te onderzoeken. Deze combinatie (lichaamsbewustzijnsstoornissen met weinig comorbide stoornissen) is niet veelvoorkomend, waardoor er niet veel bekend is over de onderliggende mechanismen achter lichaamsbewustzijnsstoornissen. Beide patiënten onderzoeken we met een soortgelijke methode, de rubberen hand illusie (RHI). De RHI is een welbekende illusie waarbij, door gelijktijdig over een zichtbare rubberen hand en de verborgen eigen hand te wrijven, de ervaring wordt opgewekt dat de aanraking die de proefpersoon voelt op de rubberen hand plaatsvindt, alsof de rubberen hand bij het lichaam van de proefpersoon hoort. Met deze illusie kan de sterkte van de illusie een indicatie zijn hoe gevoelig mensen zijn om een vreemde, niet eigen hand, een onderdeel te laten worden van het lichaamsbeeld. De twee casestudies laten zien dat beide patiënten zeer vatbaar waren voor deze illusie, vergeleken met de niet-aangedane hand (hoofdstuk 3) en vergeleken met gezonde controlegroep (hoofdstuk 4). Het lijkt er dus op dat patiënten met lichaamsbewustzijnsstoornissen meer geneigd zijn om een vreemde, rubberen arm een onderdeel te laten worden van hun lichaamsbeeld. Ten tweede lijken beide patiënten sterk gericht op visuele input en minder te profiteren van multisensorische (tactiele en visuele) stimulatie. Dat wil zeggen, beide patiënten vertonen een sterke illusie tijdens synchrone, multisensorische stimulatie, maar ook als ze alleen de vreemde arm zien (hoofdstuk 4) of wanneer multisensorische stimulatie niet synchroon was (hoofdstuk 3). Deze resultaten suggereren dat beide patiënten minder baat hebben bij multisensorische integratie ten opzichte van gezonde mensen, of ten opzichte van de arm waar ze geen problemen met bewustzijn ervaren. Deze bevindingen dragen bij tot een beter begrip van de cognitieve mechanismen die ten grondslag liggen problemen in het lichaamsbewustzijn, die daarmee kunnen leiden tot verbetering van het diagnostische proces.

In **hoofdstuk 5** hebben we de literatuur bestudeerd over de effecten van aanraking op stoornissen in de tast- en lichaamswaarneming. In deze studies is gekeken of mensen met problemen in de tastwaarneming beter in staat zijn om tast waar te nemen dan om waar te nemen wanneer iemand anders hen aanraakt. Er is echter maar klein aantal studies waarin de effecten van deze zelf-aanraking op lichaamswaarneming werd onderzocht. Hierin worden wat aanwijzingen gevonden dat zelf-aanraking de structurele lichaamsrepresentatie kan beïnvloeden. In hoofdstuk 5 onderzoek ik ook of deze zelf-aanraking effect kan hebben op somatoparaphrenie, een ernstige vorm van een lichaamsbewustzijnsstoornis waarbij de patiënt het waanidee heeft dat zijn eigen arm van iemand anders is. Dit onderzoek laat zien dat dit wel degelijk het geval is, en dat deze zelf-aanraking leidt tot een meer positief gevoel over de eigen arm, en de problemen in het lichaamsbewustzijn ook iets verminderen. Opvallend is dat ik bij deze patiënt, evenals bij andere patiënten, soortgelijke problemen hebben gezien, waarbij er vaak een neiging ontstaat de aangedane arm veelvuldig arm aan te raken. Deze studie draagt bij aan het bewijs dat dit wel degelijk nuttig kan zijn, en dat dit kan lijden tot een vermindering van de lichaamsbewustzijnsstoornis. Uit de observaties van deze patiënten valt op dat zelf-aanraking vaak op een voorzichtige, bijna liefkozende manier gebeurt. Zoals bovengenoemde patiënt zei: "Ik moet een beetje lief zijn voor die arm, zodat hij weer bij mij wil horen". Deze observaties hebben geleid tot een onderzoek gericht op dit aspect; de affectieve, aangename aanraking. Aangename aanraking wordt verwerkt door een systeem dat anatomisch en functioneel verschilt van reguliere aanraking (Gordon et al., 2011; McGlone et al., 2007; Morrison et al., 2010; Olausson et al., 2002). Dit systeem wordt aangesproken wanneer de aanraking licht en zacht is, en een snelheid heeft variërend tussen 1-10 cm/s. Deze aanraking wordt beschouwd als meest aangenaam, en wordt verwerkt door zogenaamde *C-tactile-fibers* die de informatie projecteren naar de insula cortex in plaats van naar de primaire somatosensorische cortex die bij reguliere aanraking sterk betrokken is**.** In **hoofdstuk 6** wordt een experiment beschreven waarin onderzocht wordt of affectieve, aangename aanraking een groter effect heeft op lichaamsbewustzijn in vergelijking met normale aanraking in een gezonde populatie. We vonden inderdaad dat een aangename aanraking een sterker effect had op de RHI dan normale aanraking bij gezonde proefpersonen. Dat wil zeggen dat de aanraking die werd beschouwd als het meest aangenaam, maakt de deelnemers ontvankelijker voor het accepteren van een vreemde hand in hun lichaamsbeeld. Dit werd teruggevonden op de proprioceptieve verschuiving, wat betekent dat geschatte positie van hun eigen hand een sterkere verplaatsing vertoonde richting de rubberen hand, ten opzichte van wanneer de illusie werd opgewekt met reguliere aanraking. In een van de experimenten vonden we ook een temperatuurdaling van de echte hand, maar dit konden we in een tweede experiment niet repliceren. Een verlaging van de temperatuur van de hand als uitkomstmaat van de RHI is eerder door Moseley en collega's (2008) beschreven en wordt geassocieerd met een verlaging van bewustzijn van de hand waar de illusie bij wordt opgewekt. Studies van onze en andere labs hebben echter inconsistente resultaten gevonden. In **hoofdstuk 7** analyseerden we alle gegevens die in ons lab werden verzameld over de invloed van de RHI op de temperatuur van de hand en vonden geen consistent bewijs voor koeling van de hand na de inductie van de RHI. Dit suggereert dat een temperatuurdaling geen betrouwbare uitkomstmaat is van de RHI. Aangename aanraking lijkt daarom wel de proprioceptieve verschuiving te beïnvloeden, maar niet de subjectieve ervaring of de temperatuur van de hand.

Op basis van onze resultaten kan worden geconcludeerd dat met name de aangename component van aanraking (dat de *c-tactile fibers* activeert) de lichaamsrepresentatie beïnvloedt. Deze bevinding werpt nieuw licht op de bestaande theorieën over de functionele relevantie van het *c-tactile* systeem. Van het c-tactiele systeem werd eerder al gedacht dat het sociale en affiliatieve functies heeft. Zo is al bekend dat streling door een partner bijvoorbeeld de hartslag, bloeddruk en hormoonafgifte kan verminderen (Ditzen et al., 2007; Grewen et al., 2003) en dat aanraking van zuigelingen met een laag geboortegewicht de visueel-motorische vaardigheden verbetert (Weiss et al., 2004). Ook is er recent aangetoond dat de amplitude van hersengolven verhoogd wordt wanneer premature baby's licht worden aangeraakt (Maitre et al., 2017). De bevindingen in de huidige studie laten zien dat aangename aanraking daar boven op ook invloed heeft op het lichaamsbewustzijn. Een verklaring voor dit effect kan zijn dat prettig contact de hoeveelheid somatosensorische (tast) input versterkt. Omdat aangename aanraking via andere kanalen in het perifere en centrale zenuwstelsel wordt verwerkt, zou het kunnen zijn dat er netto meer input over aanraking binnenkomt, waardoor er meer informatie beschikbaar is over het lichaam. Een vervolgexperiment waarbij aangename aanraking vervangen kan worden door pijnlijke aanraking zou kunnen uitwijzen of deze hypothese klopt.

Een klinische consequentie van de bevinding dat aangename aanraking het lichaamsbewustzijn verhoogt, is dat het een basis biedt om behandeling van lichaamsbewustzijnsstoornissen verder te ontwikkelen. Klinische observaties van patiënten met lichaamsbewustzijnsstoornissen laten zien dat patiënten de neiging hebben om de aangedane arm zachtjes te aaien en strelen, zelfs wanneer er sprake is van verlies van de sensorische functie (zoals beschreven in hoofdstuk 5). Interessant is dat, hoewel patiënten melden dat het strelen niet wordt waargenomen (althans niet op de aangedane arm), de resultaten suggereren dat dit feitelijk leidt tot verbeteringen in het lichamelijk bewustzijn. Naast de neurologische ziektebeelden, worden stoornissen in het lichaamsbewustzijn of in lichaamsrepresentatie ook gevonden in psychiatrische ziektebeelden, zoals anorexia nervosa of body integretity identity disorders. Toekomstige studies zouden moeten uitwijzen of aangename aanraking een rol van betekenis kan hebben in de verbetering hiervan.

Tenslotte wordt in **hoofdstuk 8** onderzocht welke invloed het somatosensorische systeem heeft op andere cognitieve stoornissen, in het bijzonder links-rechts verwarring. Links- rechts verwarring kan voorkomen in zowel gezonde mensen als in mensen met hersenletsel. Links-rechts verwarring na hersenletsel kan veroorzaakt worden door verschillende problemen. Zo kan een taalstoornis ervoor zorgen dat de betekenis van de termen 'links' en 'rechts' verloren is gegaan. Ook problemen in de orientatie in de ruimte kunnen het onderscheid tussen links en rechts bemoeilijken. In hoofdstuk 8 wordt onderzocht in hoeverre stoornissen in het somatosensorisch functioneren (van primaire- tot hogere orde stoornissen) invloed hebben op links- rechts verwarring. Er werden 47 mensen onderzocht in de sub-acute fase na een beroerte. In dit onderzoek heb ik gekeken of er links rechts verwarring bestond door middel van de prestatie op de *Bergen Right Left Discrimination* test. In deze test moesten mensen de linker of rechterzijde van een getekend poppetje aankruisen, en moeten dit zo snel mogelijk doen. Deze poppetjes staan in verschillende posities, wat ook betekende dat je soms het poppetje mentaal moest roteren om goed te kunnen beoordelen wat de linker of rechter hand was. Deze zelfde test werd gedaan bij een gezonde controlgroep. Naast de test gericht op links- rechts verwarring zijn alle patienten ook onderzocht op problemen in de primaire en hogere orde somatosensorische waarneming. Hiermee probeerden we inzicht te krijgen in de relatie tussen links- rechts verwarring en stoornissen in het somatosensorische systeem. De eerste bevinding was dat er bij 6 van de 47 patienten sprake was van een een probleem in het lichaamsbewustzijn. Ten tweede toonde deze studie aan dat stoornissen in de hogere orde aspecten van het somatosenorische systeem geassocieerd waren met links- rechts verwarring. Specifiek werd gevonden dat stoornissen in de structurele lichaamsrepresentatie (vingeragnosie) en lichaamsbewustzijnsstoornissen links rechtsverwarring voorspelden. Met name wanneer poppetjes mentaal geroteerd moesten worden, waren stoornissen in de hogere orde in het somatosensorisch systeem het sterkst voorspellend. Ten slotte is er een *Voxel-based lesion symptom mapping* (VLSM) analyse uitgevoerd. Deze analyse methode bekijkt de relatie tussen stoornissen op gedragsniveau en de lokatie van de beschadiging in de hersenen. De VLSM-analyse toonde een significante associatie aan tussen links rechts verwarring en schade aan de rechter insula cortex. Interssant hierbij is dat de insula cortex in eerdere studies geassocieerd wordt met interoceptieve waarneming en lichaamsbewustzijn. Deze studie laat zien dat het veranderen van perspectief (door middel van mentaal roteren) en de lichaamsrepresentatie en lichaamsbewustzijn nauw met elkaar verbonden zijn, en dat de rechter insula cortex een belangrijk gebied is dat deze functies medieert.

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Curriculum Vitae

Haike van Stralen was born in Leusden, the Netherlands on April 22nd 1983. After graduating from secondary school at the 'sgz Amersfoortse Berg', she obtained her propedeuse in Applied Psychology and went on to study Psychology. She combined professional swimming with undergraduation, in which she became highly interested in the scientic research as well as the clinical aspects of neuropsychology. After obtaining her Bachelor's degree, she combined the academic master Neuropsychology with the research master Neuroscience & Cognition and graduated both cum laude. She contiunued to combine clinical neuropscyhology and research by starting the Post-Master's Healthcare Training ("GZ-opleiding") under supervision of Martine van Zandvoort, and her PhD-research with Chris Dijkerman, Jaap Kappelle and Martine van Zandvoort. She is currently working as a healthcare psychologist in training for clinical neuropsychologist at the Department of Rehabilitation, University Medical Centre, Utrecht.

Dankwoord

Allereerst wil ik de proefpersonen bedanken die hebben meegewerkt. Vooral de vele patiënten die hebben meegedaan; veel dank voor jullie inzet en openheid over jullie klachten, ervaringen en inzichten. Dit heeft bij mij geleid tot nieuwe hypotheses en nieuwe onderzoeksvragen, waardoor dit proefschrift er heel anders uit is gaan zien dan ik van tevoren had kunnen denken.

Chris, jouw theoretische kennis is ongeëvenaard, net als jouw enthousiasme tijdens het bespreken van nieuwe onderzoekideeën of resultaten. En wat hebben we veel onderzoeksideeën gehad! Vanaf het eerste moment heb je mij veel vertrouwen en ruimte gegeven om deze onderzoeksideeën uit te denken en uit te voeren. Je hebt hierin ook altijd oog gehad voor mijn eigen wensen, waardoor ik de mogelijkheid heb gehad om het wetenschappelijk onderzoek te kunnen combineren met de kliniek. Martine, jouw talent om verbindingen te leggen tussen onderwerpen, tussen problemen en oplossingen, en tussen de wetenschap en klinische praktijk, is zeldzaam. Ik ben trots op de ontwikkeling die ik heb doorgemaakt. Ik realiseer me dat al deze ontwikkeling door jou mogelijk zijn gemaakt en ben je daar enorm dankbaar voor. Jaap, ik heb veel gehad aan je hulp met het kaderen van de studies, je kennis en je betrokkenheid. Hierdoor had ik tijdens overleggen ineens meer helderheid over de prioriteiten en kon ik beter keuzes maken in wat ik wel en niet moest doen. Bedankt voor de fijne samenwerking!

Mijn afgelopen jaren zijn vele malen leuker geweest dankzij ons team, en de (voormalig) leden van het Dijkermanlab. Miranda en Alyanne, wat fijn om jullie als deel- (lot)genoten te hebben gehad. En wat ben ik er trots op dat de eindstreep voor ons alledrie in zicht is! Onbegrijpelijk eigenlijk, gezien onze grote moeite om een stilte-uur ononderbroken te volbrengen. Alyanne, bedankt voor de fijne samenwerking. Van een mini-college over Bayesiaanse statistiek (ik heb wel een opfriscursus nodig!), tot een road-trip door Engeland, met uiteindelijk een fantastisch review artikel als resultaat. Miranda, je brengt ongekend veel sfeer met je mee. En wat hebben we veel slechte grappen gemaakt (hoewel we ze zelf wel vrij briljant vonden). Ik ben blij dat onze case-study laat zien dat we ook inhoudelijk met elkaar kunnen lezen en schrijven. Nathan, je evenwichtigheid en capaciteit om mensen en groepen te verbinden is van grote waarde. Bedankt voor de fijne samenwerking, hopelijk weten we deze voort te zetten! Rudmer, hoewel je al eventjes bij ons weg bent hoor je nog steeds bij het team. Dank voor je scherpte (vrijheidsgraden, vrijheidsgraden, vrijheidsgraden), je relativeringsvermogen en je *epic fail* woordgrappen. Ik mis de Vrijdag Faaldag met ons team! Ook ben ik jou, Dennis, dank verschuldigd voor al je hulp in het ondersteunen in experimentele opstellingen. Manasa and Kayla, thank you for all your kindness, genuine interest and constructive input. Anouk, Helen en Maartje, jullie als voorgangers hebben de lat hoog gelegd voor ons als opvolgers. Wat goed om te zien dat jullie alledrie grote sprongen voorwaarts blijven maken. Stefan, dank voor het altijd beschikbaar zijn om mee te denken of feedback te geven. De snelheid waarmee je dat doet ("Is het goed als ik er morgen naar kijk of is dat te laat?") zorgde altijd voor een enorme boost.

Ik heb het geluk gehad mijn promotietraject te mogen combineren met een opleiding tot GZ-psycholoog, en nu mijn opleiding tot Klinisch Neuropsycholoog. Ik had mij geen inhoudelijk sterker team kunnen wensen als de leden van de U-fibers; Martine, Esther, Kim, Carla, Helen, Sarai, Irene, Annelies, Mariska, en Josje. Gelukkig dat in onze groep vragen over het construct droogmolen even serieus genomen worden als vragen over het construct dementie. Ik ben er trots op dat ik mij bevind in een gezelschap van zoveel sterke klinisch neuropsychologen! Dit geldt ook voor het gezelschap opleidingsgenoten, de KNP16'ers; Anne, Annelies, Ellen, Elly, Eric, Hanneke, Iris, Jitske, Maaike, Mandy, Mariska, Marthe, Mike, Mirjam, Pieter, Rients, Sandra, en natuurlijk ook Lineke en Marije. Ik ben altijd blij als ik naar de opleiding mag, en dit komt voor een groot deel door de fijne sfeer en onze onderlinge betrokkenheid.

Het combineren van wetenschap en klinische zorg had ik niet gekund zonder daar de ruimte voor te krijgen van het team Revalidatie, Fysiotherapiewetenschap en Sport van het UMCU, in het bijzonder van Anne en Janneke. Anne, bedankt voor al je vertrouwen en je aanmoediging mij te blijven ontwikkelen, en nog meer verbinding te leggen tussen wetenschap en klinische zorg. Je enthousiasme voor cognitie en je compassie voor patiënten hebben mij gestimuleerd om net iedere keer weer een stapje harder te lopen. Janneke, je bent gericht op ontwikkeling en vernieuwing. Door je pragmatische kijk, biedt je altijd onmiddelijk tal van oplossingen bij problemen. En lieve collega's van het 'neuro-team'; Alessa, Anita, Annette, Bea, Ben, Carine, Carolien, David (onze studie staat erin!), Dyta, Esther D, Esther K, Japie, Jaqueline, Jonna, Linda, Lonneke, Merlijn, Maaike, Marie-José, Marieke, Marijke, Maurits, Rinske, Tjamke, Vera en Willeke. Bedankt voor jullie support, warmte en de ruimte om te mogen leren. En natuurlijk Ilse, bedankt voor het lenen van De Hand! Lonneke en Joke, wat fijn dat we onze krachten bundelen, elkaar steunen en helpen ontwikkelen! Nanda, de vanzelfsprekendheid waarmee jij je betrokkenheid toont en je aandacht hebt voor de kleine dingen hebben voor mij veel verschil gemaakt.

Door Sylco kreeg ik er ineens een hele familie bij. En gelukkig een hele fijne! Lieve Frank, Riny, Bauke, Sophie, Robbert, Teun, Cas, Gaby en Puck. Bedankt voor jullie betrokkenheid, gezelligheid en jullie lieve zorg voor Malin en Lou. En dank voor de fijne uitjes en etentjes

Paul, Mary, Tony (dank voor je tijd als proefpersoon!), Eveline, Peter, Lill, Ivo, Sanne, Niek en Linda. Ook had ik de fijne avonden met Willem en Anke niet willen missen. Thomas en Nadia, met jullie voelt het al snel als vakantie. Hopelijk volgen er nog vele leuke weekenden of weken samen.

Mijn buren op de Verhoevenstraat hebben altijd voor de nodige ontspanning gezorgd in stressvolle tijden. Dank voor de lekkere koffie's, de fijne borrels en de goede muziek (melodieuze techno of gewoon snoeiharde white-noise). En voor de opvang voor onze kinderen op momenten dat we het nodig hadden. Sander, bedankt dat ik gebruik heb mogen maken van jouw creatieve brein; ik werd ineens trots op het eindproduct.

Dit proefschrift had zeer waarschijnlijk een aantal hoofdstukken méér gehad wanneer ik niet mijn fijne vrienden zou hebben gehad waarmee ik zoveel leuke dingen heb gedaan. Anne, Annemarijn, Claudia, Judy, Jolande, Rianne en Shanti. Dank voor zoveel fijne feestjes, kleine borrels, grote borrels, serieuze gesprekken, goeie festivals en vele vakanties. Judy, wanneer ik jou heb gezien, kom ik altijd met meer energie *en* meer stof tot nadenken thuis. Dank voor je hulp met mijn proefschrift. Hierbij heeft je inhoudelijke feedback geholpen maar vooral je relativeringsvermogen ("Niemand, echt niemand leest je discussie"). Lieve Clau, ik begrijp nog steeds niet hoe het komt dat jij het verste weg woont, maar toch altijd het beste op de hoogte bent. Ongetwijfeld komt dit door je vermogen om vragen al gesteld te hebben voordat het onderwerp aan de orde is. Dat ik met niemand zo vaak op vakantie bent geweest als met jou, geeft wel aan hoe erg ik mij op mijn gemak voel bij jou. Ik ben dan ook heel blij dat jij degene bent die tijdens de verdediging naast mij staat. En lieve PBC'ers; Ellen, Hanneke, Marrit en Sabrina; Een boekenclub oprichten en dan nooit een boek lezen is een heel goed idee gebleken. Dank voor de leuke en leerzame avonden!

Een promotietraject heeft aanzienlijk meer overeenkomsten met topsport dan ik altijd dacht. Het vooruit plannen, deadlines halen, samenwerken, nieuwe technieken proberen, nog eens proberen maar dan anders, presteren, evalueren en weer een stap voorwaarts zetten (of soms juist niet). Mijn zwem-matties, Casper, Etta, Maarten en Madelon; Wat fijn dat we hierover vaak aan een half woord genoeg hebben. Ad, jouw advies ("bij twijfel, gewoon doen!") zit in mijn denken verankerd, en heeft absoluut voor meer motivatie gezorgd om te gaan promoveren. Annabel, bedankt voor de fijne vriendschap, ik word altijd blij van jouw gezelschap! Nienke en Suze, bedankt voor de heerlijke dagen weg en de lieve steun. Lieve Joyce, wat jammer dat je er straks niet bij kan zijn, maar wat heb je een goede reden! Dank voor al je betrokkenheid!

Lieve Jon en Tom. Bedankt voor al jullie steun, leuke kaarten en fijne uitjes. Niet alleen tijdens mijn promotietraject, maar ook al ver daarvoor. Ik ben blij dat jullie er bij zijn op 8 juni!
Lieve Willemijn, je bent bij iedere stap geweest die ik heb gezet. Jouw scherpte, humor en betrokkenheid zorgen ervoor dat je altijd net een andere kijk hebt op zaken waardoor ik zo graag van alles met je bespreek. Zaken als carrière-keuzes, opvoed-dilemma's en andere levensvragen. Maar het liefste natuurlijk als het gaat om het eurovisie songfestival en andere guilty pleasures. Bedankt je vertrouwen in mij ("ik twijfel er geen moment aan dat jij dat proefschrift gaat af schrijven"), waardoor ik dit vertrouwen ook kreeg.

Ik begrijp niet zo goed hoe goed hoe mensen werkstukken/ spreekbeurten/ diploma’s kunnen halen zonder oudere zussen. Maar ik heb dan ook wel veel geluk gehad met de mijne. Lieve Karlijn en Maartje, jullie maken mijn leven makkelijker, maar vooral ook veel leuker. Ik ben trots op hoe ver jullie het hebben geschopt (en nog steeds schoppen). Maar het allermeeste ben ik trots hoe we in iedere fase in ons leven elkaar weer op een andere manier vinden. Dit komt ook door jullie fijne partners, Joris en Roelof. Roelof, ik had je ook graag willen bedanken als proefpersoon, maar aan *outliers* heb ik niet zoveel gehad (behalve veel plezier). Toch bedankt voor al je inzet, mogelijk dat er nog een case-study volgt.

Lieve Hans en Carla, jullie waren er altijd voor ons, waardoor wij alle kansen konden grijpen die zich aandienden. Jullie warmte en steun was vanzelfsprekend, en ik realiseer me hoe bijzonder dat is. Ik kan jullie nooit genoeg bedanken voor alle fijne momenten en de gelukkige herinneringen die ik al heb, en die nog gevormd gaan worden.

Lieve Sylco. Tijdens het bierproeven, of tijdens een *effortless* zomer ben ik zo blij dat wij samen zijn. Tijdens een moeilijke periode ben ik dat nog veel meer. Wat hebben we samen veel meegemaakt korte tijd. Ik had er niks van willen missen.

Lieve Malin en Lou; Wat een geluk!