

Arousal responses to noxious stimuli in somatoparaphrenia and anosognosia: clues to body awareness

Daniele Romano,¹ Martina Gandola,² Gabriella Bottini^{2,3} and Angelo Maravita¹

1 Department of Psychology, Università degli Studi di Milano-Bicocca, Milan, Italy

2 Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy

3 Cognitive Neuropsychology Centre, Niguarda Ca' Granda Hospital, Milano, Italy

Correspondence to: Angelo Maravita,
Piazza Ateneo Nuovo 1, 20126 Milano, Italy
E-mail: angelo.maravita@unimib.it

A complex brain representation of our body allows us to monitor incoming sensory stimuli and plan actions towards the external world. A critical element of such a complex representation is the sense of ownership towards our own body parts. Brain damage may disrupt this representation, leading to the striking neuropsychological condition called somatoparaphrenia, that is, the delusion that one's own limbs belong to someone else. The clinical features characterizing somatoparaphrenia are well known, however, physiological clues of the level at which this condition may disrupt sensory functions are unknown. In the present study we investigated this issue by measuring the anticipatory skin conductance response to noxious stimuli approaching either the affected or the intact body side in a group of patients with somatoparaphrenia ($n = 5$; three females, age range = 66–84), and in a group of patients with anosognosia for sensory deficits, i.e. preserved ownership but decreased awareness of somatosensory deficit, ($n = 5$; one female, age range = 62–81 years) and in a group of purely hemiplegic patients ($n = 5$; two females, age range = 63–74 years) with no deficits of ownership or sensory awareness. Results show that anticipatory skin conductance responses to noxious stimuli directed to the contralesional hand are significantly reduced as compared to noxious stimuli directed to the ipsilesional hand in patients with somatoparaphrenia. By contrast a non-reduced anticipatory skin conductance response was observed in control participants as well as in patients affected by anosognosia for the somatosensory deficit and in patients affected by pure motor deficits. Furthermore, a pain anticipation response was always measured when the stimuli were directed towards the ipsilesional, unaffected hand in all groups. Our results show for the first time that the delusions shown by somatoparaphrenic patients are associated with an altered physiological index of perceptual analysis. The reduced response to sensory threats approaching the body suggests a deep detachment of the affected body part from the patient's body representation. Conversely, normal reactions to incoming threats are found in the presence of impaired sensory awareness but intact body ownership, supporting the notion that representation of the body may be affected at different levels following brain damage.

Keywords: somatoparaphrenia; anosognosia; skin conductance response; body representation; right brain damage

Introduction

The body, the object we know the best (de Vignemont, 2011), holds a complex and dedicated representation in the brain, being a

unique reference for our sensory-motor experience (Berlucchi and Aglioti, 1997, 2010).

Sensory experience, in particular, is deeply rooted on our body surface so that we can map stimuli at different levels of

complexity, from the most elementary signal to higher level representations referred either to the body itself or to the external space (Medina and Coslett, 2010; Medina *et al.*, 2013). Furthermore, incoming stimuli approaching the body without touching it can be interpreted as potential threats, and are constantly monitored by a sophisticated neural network. This network, including cortical areas such as the ventral intraparietal and polysensory zone, merges signals related to the somatosensory representation of the body surface with stimuli approaching from the visual space around the body, to produce defensive behaviours in case of upcoming noxious events (Cooke and Graziano, 2003; Graziano and Cooke, 2006).

Critical to a complete representation of the body is the feeling that a given body part belongs to ourselves (de Vignemont, 2011): this is typically referred to as 'sense of ownership'. Somatoparaphrenia is a neuropsychological disorder of body representation often associated with right brain lesions (Bottini *et al.*, 2002; Vallar and Ronchi, 2009; Invernizzi *et al.*, 2013) and represents a unique condition for studying the sense of ownership. Somatoparaphrenia is defined as the acquired delusion and confabulation about the contralesional side of the body (Vallar and Ronchi, 2009). Patients affected by somatoparaphrenia typically deny the ownership of their contralesional limbs, which they attribute to others, such as a nurse, doctor or their relatives (Bottini *et al.*, 2002), or even to someone else who could not possibly be there (Pugnaghi *et al.*, 2012). Somatoparaphrenia is typically found in the acute post-ictal phase after right brain damage (Gandola *et al.*, 2012), consequently limbs on the left side of the body are more often affected.

Although somatoparaphrenia holds high clinical relevance, rarely has it been the subject of formal experimental group studies (Feinberg *et al.*, 2010; Gandola *et al.*, 2012). Rather, it is often described through multiple single cases (Cogliano *et al.*, 2012; Invernizzi *et al.*, 2013), single-case or multiple single-case experimental studies (Bottini *et al.*, 2002; Fotopoulou *et al.*, 2011; van Stralen *et al.*, 2011), or anecdotal reports (Nightingale, 1982; Halligan *et al.*, 1995; Pugnaghi *et al.*, 2012).

In addition to neuropsychological studies, the sense of body ownership has been extensively investigated in several experimental studies in healthy participants, such as those involving the rubber hand illusion (Botvinick and Cohen, 1998; Tsakiris, 2010), the mirror box (Romano *et al.*, 2013), the 'full body illusion' (Ehrsson, 2007; Lenggenhager *et al.*, 2007; Ionta *et al.*, 2011), and virtual reality environments (Perez-Marcos *et al.*, 2009). Through these studies, the sense of body ownership has shown to modulate the perception and localization of sensory stimuli as well as the reaction to incoming threatening stimuli. In the rubber hand illusion paradigm, described by Botvinick and Cohen (1998), tactile strokes are delivered simultaneously to a fake arm, which is seen by the participant, and to the participant's real arm, hidden from view. This procedure induces the feeling that somatosensory stimuli are mislocalized at the location of the fake hand, and an increased feeling of ownership for that hand. The latter, which is usually assessed through subjective scales (Botvinick and Cohen, 1998; Ijsselstein *et al.*, 2006; Longo *et al.*, 2008; Petkova and Ehrsson, 2009; Bekrater-Bodmann *et al.*, 2012), typically correlates with the level of emotional activation for sudden threats directed

to the fake hand (Armel and Ramachandran, 2003; Ehrsson *et al.*, 2007; Guterstam *et al.*, 2011). Interestingly, such an increased sense of ownership for the fake hand seems to be accompanied by a relative decrease in the sense of ownership for the participant's biological hand (Moseley *et al.*, 2008; Barnsley *et al.*, 2011), although a complete agreement about this point is still lacking (de Vignemont, 2011). It is worth noting, however, that brain damage can induce much stronger feelings of body disownership than experimental manipulations in normal people, and therefore is likely to be a more informative model (de Vignemont, 2011).

A critical question, unanswered by previous experimental studies, is whether it is possible to characterize somatoparaphrenia through coherent behavioural and physiological correlates. Previous studies have shown striking behavioural modulations of somatoparaphrenic delusion. For example, one patient showed an increase in tactile sensitivity after she was told that tactile stimuli were delivered to the arm of the person to whom she was attributing the limb ownership (Bottini *et al.*, 2002). In a different study, two patients re-acquired normal ownership sensation for the contralesional hand when they looked at themselves from an allocentric perspective such as in a frontal mirror (Fotopoulou *et al.*, 2011). Moreover, it has been shown that self-touch of the contralesional impaired hand can increase the sense of ownership over it (van Stralen *et al.*, 2011). However, the physiological markers of such a striking delusion have not been investigated so far.

In the current study we sought experimental evidence that the behaviour of somatoparaphrenic patients is associated with a specific physiological response when noxious somatosensory stimuli are directed towards the limb for which patients experience a reduced sense of ownership. To this aim we measured the skin conductance response to threatening stimuli directed either towards the affected arm or towards the contralateral arm, and we compared this response with the response elicited by neutral stimuli. Given that skin conductance response can be used as a measure of the automatic affective response to approaching harmful and neutral stimuli (Lykken and Venables, 1971; Armel and Ramachandran, 2003; Guterstam *et al.*, 2011) and can be strongly modulated by the degree of ownership experienced for an external alien limb (Armel and Ramachandran, 2003; Petkova and Ehrsson, 2009; Guterstam *et al.*, 2011), we reasoned that patients with deranged ownership for contralesional limbs should show reduced, or even absent, anticipatory responses to approaching stimuli that threaten the affected limb. A similar finding would suggest that those limbs hold a deeply reduced inclusion in the patient's body representation.

Pain is a complex sensation with a multicomponent nature that includes both cognitive and sensory aspects (Iannetti and Mouraux, 2010). Notably, although nociceptive stimuli are processed through specific sensory pathways (Lenz *et al.*, 2010; Haggard *et al.*, 2013), pain experience has been shown to be modulated by attention and expectations (Babiloni *et al.*, 2008; Brown *et al.*, 2008), vision (Longo *et al.*, 2009), crossmodal signals (Gallace *et al.*, 2011), emotions (Rhudy *et al.*, 2008; Williams and Rhudy, 2009) and social factors (Avenanti *et al.*, 2010; Forgiarini *et al.*, 2011). Critically, in the current study noxious

Table 1 Main demographical and clinical features of patients

Demographic details					Neurological deficit				Anosognosia				NPS		
Patient	Age	Education (years)	Gender	Group	H	S	VF	P	H	S	VF	SP	PN	MMSE	N
p1	66	11	M	SP	2	3	3	+	1	2	2	+	–	23	+
p2	82	5	F	SP	3	3	3	+	2	2	2	+	+	21	+
p3	65	18	M	SP	3	3	3	+	0	2	0	+	–	20	+
p4	69	5	F	SP	3	3	3	+	2	2	2	+	+	20	+
p5	84	11	F	SP	3	1	3	–	0	0	1	+	+	20	+
p6	62	5	M	A	3	3	1	+	3	3	0	–	–	23	+
p7	67	17	M	A	3	3	0	+	0	3	0	–	–	21	+
p8	81	8	F	A	3	3	1	+	2	3	0	–	+	20	–
p9	77	5	M	A	1	3	1	–	0	3	0	–	–	22	+
p10	72	4	M	A	1	3	3	–	0	3	3	–	–	20	+
p11	67	5	M	H	3	0	0	–	0	0	0	–	–	25	–
p12	63	23	M	H	3	0	0	–	0	0	0	–	–	29	+
p13	65	5	F	H	3	1	0	–	0	0	0	–	–	23	–
p14	73	5	M	H	2	0	0	–	0	0	0	–	–	30	–
p15	74	11	F	H	2	1	1	–	1	0	0	–	–	25	+

NPS = neuropsychological screening; SP = somatoparaphrenia; A = anosognosia; H = motor deficit; S = somatosensation; VF = visual field; P = proprioception; PN = personal neglect; MMSE = Mini-Mental Examination Score (Folstein *et al.*, 1975); N = visual neglect; + = presence of a deficit; – = normal performance. Neurological deficit range: 0–3; 0–1 = good performance, 2 = mild deficit; 3 = severe deficit (Bisiach *et al.*, 1986). Anosognosia range 0–3; 0–1 = normal performance, 2 = mild anosognosia, 3 = severe anosognosia (Bisiach *et al.*, 1986). Each value referred to the left arm/hemisphere.

stimuli were delivered in both real and simulated conditions. In the latter crucial condition, the stimulus approached the skin, but did not actually touch the body (see 'Materials and methods' section). Simulated stimuli were introduced for studying the anticipatory response to pain (Forgiarini *et al.*, 2011), that is considered a reliable index of the purely cognitive component of pain processing (Rhudy *et al.*, 2008, 2010; Forgiarini *et al.*, 2011). Furthermore, such a condition allows us to directly compare the reaction to pain in patients, regardless of any associated somatosensory impairment.

We selected two separate control groups of patients for this study. First, a group of patients without somatoparaphrenia but presenting with anosognosia for hemianaesthesia, which is recognized as a productive symptom of disrupted body representation and usually follows right brain damage (Vallar *et al.*, 2003; Spinazzola *et al.*, 2008; Bottini *et al.*, 2009). Anosognosic patients typically deny their acquired somatosensory deficit, which is instead evident on clinical examination. Somatoparaphrenia and anosognosia for hemianaesthesia are frequently associated (i.e. somatoparaphrenic patients can still overestimate the sensory-motor ability of their contralesional limb, even if they overtly deny its ownership). However, sometimes they reflect opposite manifestations of disrupted body representation concerning somatosensory function; whereas in the former case patients deny the ownership of the impaired arm, and consequently to perceive any sensory stimulus delivered to that hand, in the latter case they overestimate their actual sensory functions. A further experimental group of hemiplegic patients (i.e. patients without any deficit of ownership or awareness) was tested to control for any unspecific effect of right brain damage on skin conductance response. For the control groups showing intact body ownership, we predicted preserved anticipatory response to painful sensations for both hands.

Materials and methods

Patients

Fifteen right-handed (evaluated with the Edinburgh Handedness Inventory: Oldfield, 1971) patients with right brain damage took part in the study (six females, age = 72.06 ± 9.2 years [mean \pm standard deviation (SD)], education = 9.2 ± 5.9 years), after giving their informed consent. They were all recruited at the Stroke Unit of Niguarda Ca' Granda Hospital in Milan. The experiment was conducted according to the principles of the Declaration of Helsinki (World Medical Organization, 1996) and was approved by the ethical committee of the hospital.

Patients were divided into three groups of five individuals each, according to their clinical diagnosis, namely: somatoparaphrenia (three females, age = 73.2 ± 9 , education = 10 ± 5.4 years); anosognosia for somatosensory deficit (one female, age = 74.6 ± 4.3 , education = 7.8 ± 5.4 years) and left hemiplegia without anosognosia and without somatoparaphrenia (two females, age = 68.4 ± 4.9 , education = 9.8 ± 7.8 years).

Patients were at their first stroke event in the acute or subacute phase (<30 days from the stroke) and none reported any previous neurological or psychiatric disease nor presented with general confusional state.

The main biographic and clinical details of patients are reported in Table 1.

Neurological assessment

Each patient underwent a standardized neurological assessment of basic motor, somatosensory and visual functions according to the procedure outlined by Bisiach *et al.* (1986).

Furthermore, we performed a preliminary somatosensory test using the experimental painful and neutral stimuli (see below). We delivered

(in a random sequence) three stimulations for each stimulus type on either hand, plus three additional catch trials, with the same setup used for the experimental procedure (see below). During this evaluation patients were blindfolded and were asked to report each stimulus. Patients with anosognosia and somatoparaphrenia did not detect any tactile or painful stimulation on the left hand, whereas hemiplegic patients had flawless performance.

To test proprioception, the examiner placed the patient's impaired hand in two different positions (palm up and palm down) 10 times. At each time, the patient was asked to place his/her unimpaired hand in the same position, while keeping his/her eyes closed. Proprioception was also tested by positioning the patient's contralesional index finger in two different positions (up or down) 10 times and asking the patient, on each trial, to mimic that posture with the ipsilesional, homologous finger. Personal neglect was assessed following the procedure proposed by Bisiach *et al.* (1986) where the patient is asked to touch his/her left hand using the right hand.

Assessment of anosognosia

Patient's awareness of neurological deficits (i.e. anosognosia) was assessed by means of a standardized four-point scale (Bisiach *et al.*, 1986). In this scale patients score 0 (full awareness) if they report their deficit after a general question about their illness; score 1 if they report their deficit after a specific question about their strength, somatosensation or visual function; score 2 if they recognize their deficit only after it is shown by the examiner (mild anosognosia); and score 3 if the acknowledgment of the disorder cannot be achieved in any way (severe anosognosia).

Assessment of somatoparaphrenia

Somatoparaphrenia was investigated by interviewing patients about the presence of any delusional feeling referred to their contralesional upper limb. The interview started by placing the patient's contralesional left hand in front of him/her and included the following, fixed sequence of questions: 'What is this? Whose hand is this? Where is your hand? Why is there an alien hand here?'. The first question was always asked, whereas each of the following questions was proposed only if patients reported any delusion in the preceding question. Patients were considered somatoparaphrenic if they denied the ownership of the contralesional limb and attributed it to someone else (Invernizzi *et al.*, 2013) (Table 2).

Anosognosia and somatoparaphrenia were tested both during the neurological evaluation and just before the beginning of the experimental session to ensure the persistence of the specific clinical condition at the time of testing.

Neuropsychological screening

A short neuropsychological screening was performed to test for the presence of neglect, which is typically associated with somatoparaphrenia and anosognosia, and to rule out a general cognitive impairment. In the Mini-Mental State Examination (Folstein *et al.*, 1975) all patients obtained a score >20 thus discounting the presence of a severe general cognitive impairment. The assessment of neglect was performed through the Albert cancellation test (Albert, 1973) and the clock drawing test (Mondini *et al.*, 2003): 11 of 15 patients showed neglect in at least one of these tests (five somatoparaphrenic, four anosognosic and two hemiplegic patients; Table 1). For this reason the experimental paradigm was specifically designed to avoid any

Table 2 Verbalization of patients with somatoparaphrenia to the question 'Whose hand is this?'

Patient	Response to the examiner's question: 'Whose hand is this?'
p1	'It is your hand (i.e. the neuropsychologist hand), I am sure. My hand is bigger, mine is like a shovel, this is too tiny.'
p2	'This is my sister's hand, yes my sister's hand. My hand is on my belly but I am too fat I cannot see.'
p3	'I do not know. It is not mine. It is just the two of us, so I guess it is your hand (i.e. the neuropsychologist hand).'
p4	'This is my niece's hand. She works here (i.e. in the hospital), I do not know why her hand is here, she should be around.'
p5	'This is not my hand. I do not know whose hand is this. Maybe someone working here who examined me before left it here.'

possible confound as a result of neglect (see experimental procedure section below).

Lesion mapping

Brain lesions were identified by CT and mapped in the stereotactic space of the Montreal Neurological Institute (MNI) using a standard MRI volume (voxels of 1 mm³) that conformed to that stereotactic space. Lesion reconstruction was performed using the free software MRICro (Rorden and Brett, 2000; www.mricro.com). The mapping procedure included the following steps (see Gandola *et al.*, 2012 for further details): (i) adaptation of the MRI template to the patient's CT scan; (ii) lesion mapping: a skilled rater (M.G.) manually mapped the lesion onto each correspondent template slice by using anatomical landmarks. A second skilled rater (G.B.) double-checked for the accuracy of the tracings for each patient. In cases of disagreement an inter-section lesion map was used; (iii) lesion reorientation: the lesion maps were then transformed back into the standard space by using the inverse of the transformation parameters formerly used for the adaptation of the MRI template to the patient's brain scan; and (iv) lesion analysis: we used the overlay lesion plots technique and the subtraction method (Rorden and Karnath, 2004), implemented in the software MRICron (Rorden *et al.*, 2007), to illustrate differences in the distribution of the lesion between groups.

The anatomical localization of the lesions was assessed using the Automated Anatomical Labelling map (template AAL; Tzourio-Mazoyer *et al.*, 2002), which classifies the anatomical distribution of digital images in stereotactic space.

Experimental procedure

Stimuli

A series of 64 mechanical stimuli were administered to each patient in a single session and simultaneously the skin conductance response was recorded. The entire session took ~30 min.

Two types of stimuli were used: noxious stimuli (delivered through a needle) and neutral stimuli (delivered through a cotton swab) (Cheng *et al.*, 2007; Forgiarini *et al.*, 2011; Höfle *et al.*, 2012). All participants flawlessly distinguished the needle from the cotton swab both by visual inspection and during the stimulation of their ipsilesional hand without seeing it. Non-painful tactile stimuli were also introduced to record baseline responses to a neutral object approaching the skin,

useful to calculate the anticipatory response to threatening stimuli (see below) and to reduce skin conductance response adaptation, which is typically very quick in the presence of constant stimulation (Levinson and Edelberg, 1985).

Stimuli were administered under two conditions: real and simulated. In the real condition the needle and the cotton swab touched the skin of the back of the hand (between the thumb and the index finger) for ~ 0.5 s in an area of ~ 1 cm². In the simulated condition the stimulus approached the same area of the skin, but stopped at a distance of ~ 0.5 cm from the skin where the stimulus was kept still for ~ 0.5 s and then removed.

Stimuli were alternatively delivered to the ipsilesional right hand, which served as a control, or the contralesional left hand. Globally, eight different stimulation conditions were used: painful real right hand, painful real left hand, painful simulated right, painful simulated left, neutral real right, neutral real left, neutral simulated right, and neutral simulated left.

The 64 stimuli were divided into eight independent blocks of eight stimuli each (one per condition); the stimulus sequence was randomized within each block except in the first block where a pseudorandom sequence was used. In this pseudorandom sequence the first two stimuli were always neutral, followed by four noxious and two neutral ones. By doing so the two initial stimulations, where the skin conductance response is usually extremely strong because of the novelty of the situation, never included the critical noxious stimulation. In addition, this blocked procedure allowed us to control for the effect of habituation, which can occur quite rapidly, ensuring that all stimulus types were delivered within each block.

A list of stimuli was generated before each block and used by the experimenter for stimulus delivery. This allowed the examiner to know in advance which stimulus to deliver and which trigger signal to send to the skin conductance response trace for offline event-related analysis (see below). A pause was introduced after four blocks or at the end of any block if the patient asked for a rest.

Setting and procedures

Patients sat comfortably at a table in front of the experimenter with their hands resting on the table, palm down. The hands were aligned one above the other along the mid-sagittal plane, with the aim of minimizing any neglect-induced imbalance in the visual monitoring during stimulus delivery (Fig. 1). With this arrangement all patients reported to have complete vision of both hands. The hand closer to the body was the left hand for three patients and the right hand for the remaining two in each group.

Patients were then asked to relax, remain as still as possible and keep regular breathing, while gazing towards a fixation point drawn at the centre of an opaque screen, which was placed at a distance of 50 cm in front of them. The screen shielded both the experimenter's hands and the stimuli. On each trial a stimulus was presented by the experimenter (D.R.), using his right hand. The experimenter was trained to use the same trajectory for all stimuli. From the patients' point of view the stimuli emerged randomly from behind the screen and approached one of the hands, unpredictably. Patients were instructed to gaze at the stimuli for the whole trajectory.

Skin conductance response

Skin conductance response was recorded through a SC-2701 biosignal amplifier (Bioderm, UFI) connected to a PC through a serial port. The gain parameter was set at $10 \mu\text{mho}/\text{V}$; the signal was sampled at 10 Hz. The signal was acquired by means of two silver electrodes (1081 FG Skin Conductance Electrode) placed on the first phalanx of the index and ring fingers of the ipsilesional hand. A saline conductive paste was

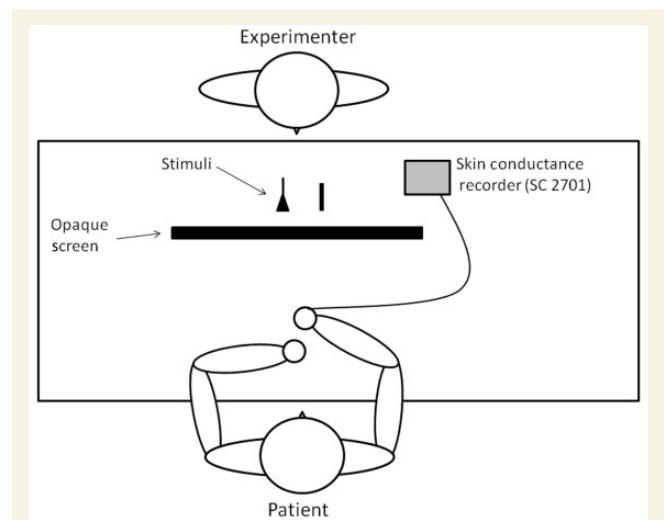


Figure 1 Schematic representation of the experimental setting. Participants sat in front of the experimenter with both hands centrally aligned. While looking at the stimuli approaching one of their two hands their skin conductance response was recorded from two electrodes connected to the right intact hand. There were two possible stimuli: a painful needle (black bar) and a neutral cotton swab (triangular shape) and could either touch the hand (real contact) or stopping just before the contact (simulated contact, assessing the anticipatory response).

applied to the electrodes to improve signal-to-noise ratio. Data were digitalized using the SC-2701 software with a resolution of 12 bit.

Data preprocessing

The analysis of skin conductance response was conducted on peak-to-base measures, as is often used to analyse skin conductance response to painful stimuli (Lykken and Venables, 1971; Ehrsson, 2007; Rhudy *et al.*, 2007, 2010; Breimhorst *et al.*, 2011). Here, in each trial, the difference between the maximum value detected in a 5-s post-stimulus time window and the baseline calculated as the average value of a 0.3 s prestimulus time window was computed.

Triggers coding for the stimulus type were manually sent to the skin conductance response trace through the computer keyboard when the stimulus emerged from behind the opaque panel and became visible to the participant.

Only responses to simulated stimuli were analysed. The reason for this choice relies on the fact that somatosensory processing may be defective to a different extent in our patients with right brain damage, and difficult to assess unequivocally due to clinical or subclinical neglect (Sterzi *et al.*, 1993; Vallar *et al.*, 2003). Accordingly, we decided to consider only responses to simulated stimuli that could be processed equally by all patients, regardless of any somatosensory deficit.

The peak-to-base responses to simulated stimuli were then normalized within-subject and converted into z-scores (Rhudy *et al.*, 2007, 2008, 2010; Williams and Rhudy, 2009) to obtain comparable measures among the patients, given the well-known large intersubject variability of skin conductance response (Lykken and Venables, 1971; Fowles *et al.*, 1981).

Data analysis

Data were analysed with SPSS 21 (IBM® SPSS®). A general linear model was used on skin conductance response data, factoring: stimulus

Table 3 ANOVA results

ANOVA results table						
Source	df	df(error)	F	P-value	η^2	Power
Group (between)	2	12	0.924	0.423	0.133	0.280
Stimulus (within)	1	12	73.846	0.000	0.860	0.999
Hand (within)	1	12	0.010	0.922	0.001	0.060
Stimulus \times Group	2	12	9.943	0.003	0.624	0.947
Hand \times Group	2	12	2.571	0.118	0.300	0.415
Stimulus \times Hand	1	12	3.741	0.077	0.238	0.765
Stimulus \times Hand \times Group	2	12	4.576	0.033	0.433	0.960

Df = degrees of freedom; F = value of the F-test statistic; η^2 = partial eta squared, effect size measure; Power = estimated achieved power.

(painful/neutral), hand (left/right), as within subject factors and group (hemiplegia/anosognosia/somatoparaphrenia) as between subject factor. This resulted in a 2 \times 2 (within) \times 3 (between) ANOVA mixed design.

Achieved power and effect size, measured with the partial eta squared (η^2), were also computed with G*Power 3.1 software (<http://www.psych.uni-duesseldorf.de/abteilungen/aap/gpower3/>). Significant interactions were explored by looking at the confidence intervals (CI), i.e. mean \pm standard error of the mean (SEM) \times *t*-critic (*t*-distribution value for the level of confidence set) (Cohen 1990, 1992, 1994; Masson and Loftus 2003), setting at 90% the confidence level. Confidence intervals show the range of probability in which data can be found in a given condition. As different experimental designs may require a slightly different use of the confidence intervals (Masson and Loftus 2003), it is worth mentioning that, in the present experimental design, when the intervals expressed by two variables do not overlap, a difference between the two variables can be assumed (Masson and Loftus, 2003).

Data were normally distributed, as witnessed by a normal range of skewness and kurtosis (all values < |1| and Kolmogorov-Smirnov *P* = non-significant) and non-significant F-tests for the equality of variance between the four conditions and the three groups.

Results

Skin conductance response results

The full ANOVA results are reported in Table 3, the interaction stimulus \times group was significant, as well as the three-level interaction between all factors of the model.

Confidence intervals show that all three groups have stronger skin conductance responses for painful than neutral stimuli, but the difference is more pronounced in the hemiplegia group [somatoparaphrenia painful = 0.048 to 0.256 (z-scores for the 90% CI), 0.152 (mean z-score); somatoparaphrenia neutral = -0.278 to -0.049, mean = -0.163; anosognosia painful = 0.127 to .335, mean = 0.231; anosognosia neutral = -0.340 to -0.111, mean = -0.225; hemiplegia painful = 0.401 to 0.609, mean = 0.505; hemiplegia neutral = -0.647 to -0.419, mean = -0.533].

Critically in the three-level interaction, confidence intervals show that responses to painful stimuli are different from neutral stimuli only in the right ipsilesional hand, in patients with somatoparaphrenia (painful right = 0.265 to 0.653, mean = 0.459; neutral

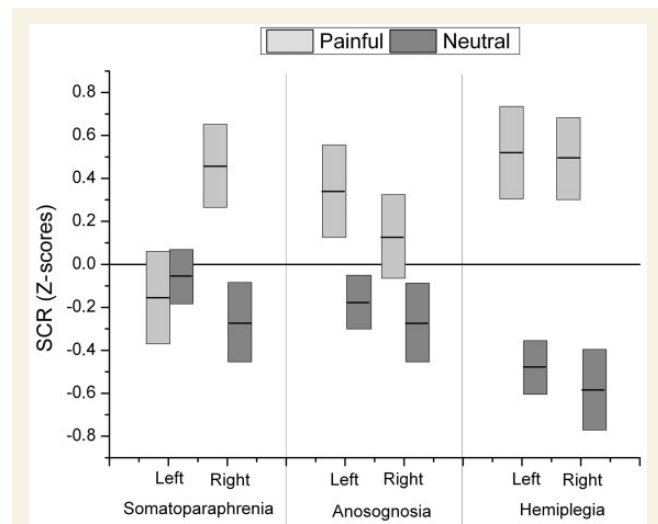


Figure 2 Skin conductance response (SCR) results of the three clinical populations to simulated painful (light grey columns) and neutral (dark grey columns) stimuli. Columns represent the 90% CIs of peak-to-base skin conductance response expressed in z-scores, horizontal bars indicate average values.

right = -0.457 to -0.087, mean = -0.272), whereas in the left impaired hand the anticipatory response to pain was lacking (painful left = -0.369 to 0.059, mean = -0.155; neutral left = -0.178 to 0.070 mean = -0.054).

In the anosognosia group confidence intervals show that the anticipatory response to pain was recordable in both hands (painful left = 0.124 to 0.552, mean = 0.338; neutral left = -0.303 to -0.055 mean = -0.179; painful right = -0.070 to 0.318, mean = 0.124; neutral right = -0.457 to -0.087, mean = -0.272).

Likewise, in the hemiplegic group we found that both hands had comparable skin conductance responses and that the response was larger for approaching painful, as compared to neutral stimuli (painful left = 0.304 to 0.732, mean = 0.518; neutral left = -0.605 to -0.358 mean = -0.482; painful right = 0.298 to 0.686, mean = 0.492; neutral right = -0.770 to -0.399, mean = -0.584) (Fig. 2). Notably, the three experimental groups showed a different frequency of personal neglect, which

was more frequently observed in the somatoparaphrenic group. To rule out a role of personal neglect in the pattern of skin conductance response in the somatoparaphrenic group, we ran a separate ANOVA factoring stimulus (pain/neutral) and hand (right/left) as within subject factors, and the presence of personal neglect (four patients with personal neglect versus 11 patients without personal neglect) as the between subject factor. The results suggest that personal neglect cannot explain our main findings, given that the three-way interaction was not significant [$F(1,13) = 0.783$, $P = 0.392$, power = 0.130, $\eta^2 = 0.057$].

Lesion mapping

All patients presented with a right brain ischaemic or haemorrhagic lesion. Two patients were excluded from the lesion mapping because CT scans were not available (Cases p3 and p12, Table 1). Figure 3 illustrates the overlay lesion plots of patients with somatoparaphrenia (Fig. 3A; $n = 4$), patients with anosognosia for the somatosensory deficit without somatoparaphrenia (Fig. 3B; $n = 5$) and patients with hemiplegia without anosognosia and without somatoparaphrenia (Fig. 3C; $n = 4$).

In patients with somatoparaphrenia the centre of the overlap (defined as those voxels that were damaged in at least three of four patients; drawn in yellow and white in Fig. 3A) is localized in the right white matter (including the posterior limb of the internal capsule and the corona radiata), in the basal ganglia (caudate, putamen and pallidum) and in the thalamus. The overlap extended into the hippocampus and the amygdala.

The lesions of patients with anosognosia for the somatosensory deficit overlapped in the right Rolandic operculum and the insula (yellow in Fig. 3B), in the basal ganglia (caudate and putamen) and in the white matter including the posterior limb of the internal capsule, the corona radiata and the external capsule.

Finally, Fig. 3C illustrates the lesion overlay in patients with left hemiplegia without anosognosia and without somatoparaphrenia. The centre of the overlap (50% of patients) is localized in the sensorimotor cortex (precentral and postcentral gyri), in the parietal, frontal and insular cortices. The white matter in the right hemisphere is also damaged.

To distinguish the brain regions frequently damaged in patients with somatoparaphrenia, but spared in patients with anosognosia for hemiplegia without feeling of disownership, we used the subtraction method (Rorden and Karnath, 2004), a good alternative to objective voxel-wise statistical analyses when the sample size is small, as in the present study.

It was found that the same regions highlighted in the lesion overlap of the patients with somatoparaphrenia (Fig. 3A) were at least 75% more frequently damaged in this group than in the anosognosic group (yellow in Fig. 4).

The subtraction analysis between patients with anosognosia for somatosensory deficits and patients with somatoparaphrenia showed that only a few voxels in the subcortical white matter, in the Rolandic operculum and in the insula were involved 55% or more frequently in the anosognosic group compared with the somatoparaphrenic group (light blue in Fig. 4).

Discussion

In the present work we sought physiological correlates of the processing of threatening stimuli in neuropsychological patients affected by somatoparaphrenia. Somatoparaphrenia typically follows a right brain lesion and is a condition in which patients feel that their paralysed limb does not belong to their body. In particular we exploited the notion that pain is a multifactorial experience depending, among other factors, on the visual analysis of incoming stimuli in relation to the mental representation of one's own body (Longo *et al.*, 2009; Gallace *et al.*, 2011; Mancini *et al.*, 2011). The monitoring of incoming threats gives rise to cognitive and emotional anticipatory reactions (Ploghaus, 1999; Brown and Jones, 2008; Clark *et al.*, 2008; Rhudy *et al.*, 2008) that alert the subject to possible noxious stimuli directed towards their own body and activate defensive behaviours (Cooke and Graziano, 2003; Graziano and Cooke, 2006). An additional response is usually observed when the painful stimulus actually contacts the skin, as an effect of somatosensory processing (Höfle *et al.*, 2012). In the present study, the response to real somatosensory stimuli was not analysed. Although this stands as a limitation of the present study, this is justified by the knowledge that the level of processing of contralateral somatosensory stimuli is difficult to assess in patients with right brain damage because of the possible contribution of neglect (Sterzi *et al.*, 1993; Vallar *et al.*, 2003), and of a variable level of implicit processing of unreported somatosensory stimuli (Vallar *et al.*, 1991). In the absence of any objective (i.e. neurophysiological) measure of somatosensory processing, with the present design the presence or lack of difference between real and simulated stimuli would be difficult to interpret. Therefore, in all our groups of patients with right brain damage, we planned skin conductance response analysis only on simulated stimuli, in which actual somatosensory stimulation is absent.

In the present study, a direct, condition by condition comparison between the groups is meaningless, given that standardized values were used, whereas general differences between groups can be observed by looking at the full pattern of responses. In all groups of patients the physiological reaction to an approaching stimulus changes depending on the salience of the stimulus, as typically found in the literature (Jensen *et al.*, 2003; Breimhorst *et al.*, 2011). In fact, the physiological reaction is stronger for noxious stimuli than for neutral tactile stimuli that approach the body.

The crucial finding of this study is that the anticipatory response to threatening stimuli is strictly dependent on the sense of ownership for the threatened body part. In particular, skin conductance response in patients with somatoparaphrenia was coherent with the referred feeling of non-belonging for their left arm (*cf.* Bottini *et al.*, 2002; Vallar and Ronchi, 2009; Pugnaghi *et al.*, 2012; Invernizzi *et al.*, 2013), being absent, or strongly reduced, when the stimulus was directed to the hand that the patient attributed to someone else. Conversely the anticipatory response was present when the stimulus was directed to the hand that they identified as their own, suggesting that the reduced response for the contralateral hand was not because of a general effect of right brain damage on skin conductance response. This possibility was also discarded by the finding of

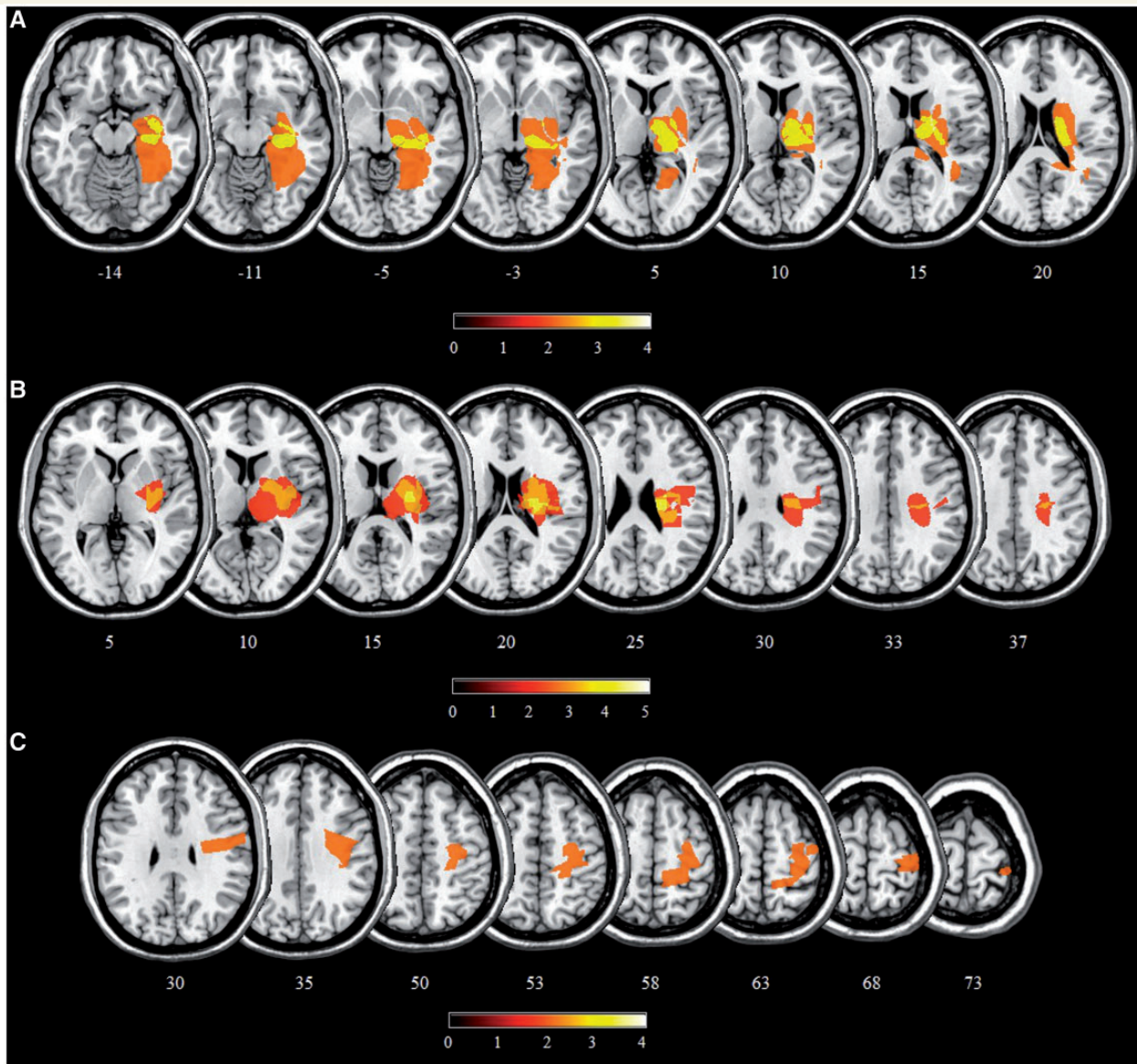


Figure 3 Lesion reconstruction of four patients with somatoparaphrenia (A), five patients with anosognosia for the somatosensory deficit (B), and four patients with hemiplegia without somatoparaphrenia or anosognosia (C). The regional frequency of brain lesion in each area is expressed according to the colour scale. MNI z-coordinates of each section are reported under each slice. Reconstructions were performed using the software MRICro.

normal anticipatory responses for stimuli directed to both hands in the two control groups of patients with right brain damage.

Recently it has been proposed that the lesions in somatoparaphrenic patients might impair the construction of a coherent body representation, selectively for a given anatomical district, to the point that patients deny the ownership of the affected limb (Berti, 2013). The present results suggest that the delusion of somatoparaphrenic patients corresponds to such a profound detachment of the affected limb from body representation that even physiological reactions to stimuli potentially dangerous for the body are reduced or abolished.

Alternatively, one could argue that patients with somatoparaphrenia did not show pain anticipation for the left arm/hand because of insensitivity to the stimuli on the left side, and not because of

disrupted body representation. If this were the case, however, we should expect that patients with anosognosia for hemianaesthesia, i.e. patients with a clear somatosensory deficit, show the same pattern of responses despite their false belief of intact somatosensory processing. By contrast, we found that anosognosic patients show an anticipatory response to noxious stimuli on both hands, congruent with the idea that patients with anosognosia are generally unable to check the truthfulness of their beliefs (Vuilleumier 2004), feeling overconfident and unable to correct them (Vocat *et al.*, 2013), in spite of intact body ownership. Our findings suggest that the delusions reported by patients are informative about the core state of their body representation and the way in which a derangement of that representation influences the prediction about incoming sensory events. In a similar fashion, patients

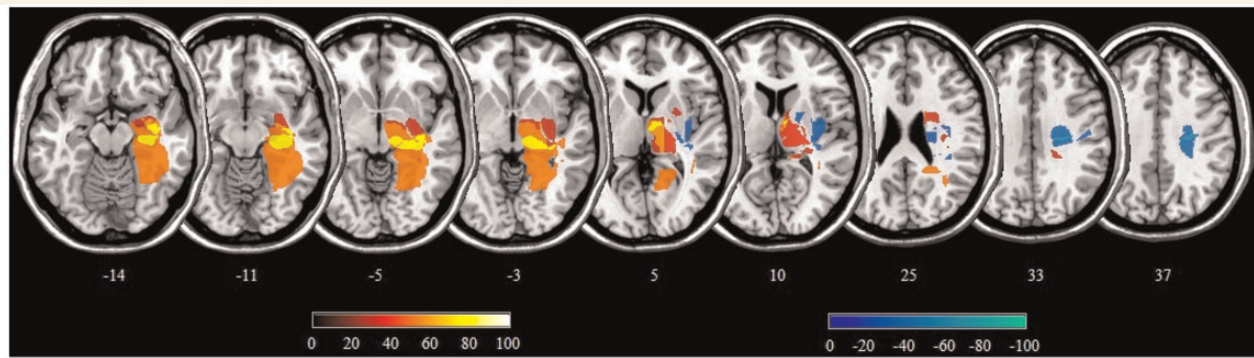


Figure 4 Subtraction analysis: patients showing somatoparaphrenia ($n = 4$) minus patients with anosognosia for hemiplegia, without somatoparaphrenia ($n = 5$). Regions frequently damaged in patients with somatoparaphrenia but spared in patients without this symptom (anosognosic group) are illustrated with warm colours, from dark red to white. Only regions that were damaged at least 50% more in the somatoparaphrenic group than in the anosognosic group are reported. The cold colours, from dark to light blue, illustrate regions more frequently damaged in patients with anosognosia without somatoparaphrenia than in patients with somatoparaphrenia. Only regions that were damaged at least 50% more in the anosognosic group than in the somatoparaphrenic group are reported. MNI z-coordinates of each section are reported under each slice. Reconstructions were performed using the software MRIcron.

with anosognosia for hemiplegia have been shown to activate motor plans coherent with their false beliefs: when performing a bimanual motor task, the motor plan for the paretic limb interferes with the movements executed with the spared hand, similar to healthy people and differently from hemiplegic patients that are aware of their motor deficit (Garbarini *et al.*, 2012). Our data are also in line with recent findings on stroke patients who show the peculiar tendency to erroneously attribute someone else's limb to themselves. Those patients judge noxious stimuli directed towards the misattributed external limb as painful as those directed to their own limb (Pia *et al.*, 2013). However the direct matching of these behavioural results with our results remains speculative as a direct trial by trial comparison between behavioural and physiological responses was not performed.

The present results are reminiscent of the results obtained in healthy participants after the induction of bodily illusions. In the rubber hand illusion, where the feeling that a fake hand belongs to one's own body rises from congruent visuo-tactile stimulations on the fake and the participant's hand (Botvinick and Cohen, 1998; Tsakiris, 2010; Rohde *et al.*, 2011), has been well established that the more the feeling of embodiment of the rubber hand the more the autonomic activation for an unexpected threatening stimulus directed to that fake hand, suggesting that ownership feelings are relevant to determine anticipatory autonomic responses (Armel and Ramachandran, 2003; Guterstam *et al.*, 2011).

Further clues about the nature of the deficit in our patients can be gathered from the anatomical analysis of brain lesions (even if these data warrant great interpretative caution, given that the small sample size did not allow statistical analysis). The distribution of the brain lesions of patients with somatoparaphrenia confirms the anatomical pattern previously associated with this disorder (Gandola *et al.*, 2012; Invernizzi *et al.*, 2013; Jenkinson *et al.*, 2013). The four patients with somatoparaphrenia for which we could reconstruct brain lesions had lesions overlapping in the subcortical white matter of the right hemisphere, in the basal ganglia

and in the limbic circuit (i.e. hippocampus and amygdala). This localization pattern, which is predominantly subcortical, may cause a deficit in integrating bottom-up information with higher-order body representation, with a consequent feeling of disownership for that part of the body (Zeller *et al.*, 2011; Gandola *et al.*, 2012). Furthermore, the lesions of the right hippocampus and amygdala may reduce the sense of familiarity for the affected body part (Gandola *et al.*, 2012) and contribute to the reduction of the emotional response to approaching threatening stimuli.

Four of five patients with anosognosia for somatosensation presented a lesion of the insular cortex, basal ganglia and periventricular white matter, in agreement with the observation of Spinazzola *et al.* (2008) (Fig. 3b). In patients with anosognosia the sense of body ownership was not impaired and the anticipatory response to pain was still present. This observation is particularly interesting because it suggests that, in patients with equivalent sensory impairment (all but one patient, Case p5, Table 1, in both groups presented a severe left hemianaesthesia, as assessed with the standardized neurological procedure), an anticipatory response to pain is preserved only if the lesion did not affect the sense of body ownership. Finally, the lesions of patients with hemiplegia did not impair body ownership for the paretic limb, as well as the emotional responses to pain.

Conclusion

Our data suggest that patients affected by disrupted ownership for contralesional limbs show a reduced monitoring of incoming threatening stimuli when these stimuli are directed towards the affected body part.

This finding selectively holds for patients with somatoparaphrenia, and not for those with anosognosia, thus confirming that the level of processing at which bodily consciousness is impaired in these two clinical conditions is very different, even if they are both frequently associated with right brain damage and often

occur together. Although the use of small groups imposes some cautions in the generalization of the results, still the present work represents one of the few efforts, present in the literature, to use a group study approach in the investigation of somatoparaphrenia. The present work provides the first demonstration of a physiological correlate of somatoparaphrenia. The skin conductance response pattern of somatoparaphrenic patients reflects a profound modification of automatic arousal responses to threats directed towards the affected limbs. Furthermore, we can speculate that somatoparaphrenia may correspond not only to a disruption of body representation, but also to a more general alteration of body/space interactions, which includes a relevant reduction in the reactivity to harmful stimuli. In line with the concept of a 'safety region' surrounding our body [or 'flight zone', as outlined by Hediger (1955)], somatoparaphrenia may reduce the monitoring of that region of space, also with the contribution of other coexisting neuropsychological deficits, such as neglect, thus significantly impairing the patients' interaction with the world around them. This suggests that specific attention should be paid to somatoparaphrenic patients in the clinical environment, given the highly protective value of monitoring peripersonal space for incoming threats. This is particularly relevant for patients with deficits of bodily awareness that are less evident than somatoparaphrenia, such as the case of asomatognosia, i.e. the unawareness of one's own body parts (Zeller *et al.*, 2011) or with subclinical impairments that are likely to go undiagnosed (Baier and Karnath, 2008).

Acknowledgements

We would like to thank Francesco Marini and Annalisa Benetello for their helpful comments and suggestions on an early version of this manuscript.

References

- Albert ML. A simple test of visual neglect. *Neurology* 1973; 23: 658–64.
- Armstrong KC, Ramachandran VS. Projecting sensations to external objects: evidence from skin conductance response. *Proc R Soc B* 2003; 270: 1499–506.
- Baier B, Karnath HO. Tight link between our sense of limb ownership and self-awareness of actions. *Stroke* 2008; 39: 486–8.
- Barnsley N, McAuley JH, Mohan R, Dey A, Thomas P, Moseley GL. The rubber hand illusion increases histamine reactivity in the real arm. *Curr Biol* 2011; 21: R945–46.
- Bekrater-Bodmann R, Foell J, Diers M, Flor H. The perceptual and neuronal stability of the rubber hand illusion across contexts and over time. *Brain Res* 2012; 1452: 130–9.
- Berlucchi G, Aglioti S. The body in the brain: neural bases of corporeal awareness. *Trends Neurosci* 1997; 20: 560–4.
- Berlucchi G, Aglioti S. The body in the brain revisited. *Exp Brain Res* 2010; 200: 25–35.
- Berti A. This limb is mine but I do not want it: from anatomy to body ownership. *Brain* 2013; 136: 11–13.
- Bisiach E, Vallar G, Perani D, Papagno C, Berti A, Bisiach E. Unawareness of disease following lesions of the right hemisphere: anosognosia for hemiplegia and anosognosia for hemianopia. *Neuropsychologia* 1986; 24: 471–82.
- Bottini G, Bisiach E, Sterzi R, Vallar G. Feeling touches in someone else's hand. *Neuroreport* 2002; 13: 249–52.
- Bottini G, Sedda A, Ferrè ER, Invernizzi P, Gandola M, Paulesu E. Productive symptoms in right brain damage. *Curr Opin Neurol* 2009; 22: 589–93.
- Botvinick M, Cohen J. Rubber hands "feel" touch that eyes see. *Nature* 1998; 391: 756.
- Breimhorst M, Sandrock S, Fechir M, Hausenblas N, Geber C, Birklein F. Do intensity ratings and skin conductance responses reliably discriminate between different stimulus intensities in experimentally induced pain? *J Pain* 2011; 12: 61–70.
- Brown CA, Jones AKP. A role for midcingulate cortex in the interruptive effects of pain anticipation on attention. *Clin Neurophysiol* 2008; 119: 2370–9.
- Brown CA, Seymour B, El-Dereby W, Jones AKP. Confidence in beliefs about pain predicts expectancy effects on pain perception and anticipatory processing in right anterior insula. *Pain* 2008; 139: 324–32.
- Cheng Y, Lin C, Liu H, Hsu Y, Lim K, Hung D, et al. Expertise modulates the perception of pain in others. *Curr Biol* 2007; 17: 1708–13.
- Clark JA, Brown CA, Jones AKP, El-Dereby W. Dissociating nociceptive modulation by the duration of pain anticipation from unpredictability in the timing of pain. *Clin Neurophysiol* 2008; 119: 2870–8.
- Cogliano R, Crisci C, Conson M, Grossi D, Trojano L. Chronic somatoparaphrenia: a follow-up study on two clinical cases. *Cortex* 2012; 48: 758–67.
- Cohen J. Things I have learned (So far). *Am Psychol* 1990; 45: 1304–12.
- Cohen J. A power primer. *Psychol Bull* 1992; 112: 155–9.
- Cohen J. The earth is round ($p < .05$). *Am Psychol* 1994; 49: 997–1003.
- Cooke DF, Graziano MS. Defensive movements evoked by air puff in monkeys. *J Neurophysiol* 2003; 90: 3317–29.
- de Vignemont F. Embodiment, ownership and disownership. *Conscious Cogn* 2011; 20: 82–93.
- Ehrsson HH. The experimental induction of out-of-body experiences. *Science* 2007; 317: 1048.
- Ehrsson HH, Wiech K, Weiskopf N, Dolan RJ, Passingham RE. Threatening a rubber hand that you feel is yours elicits a cortical anxiety response. *Proc Natl Acad Sci USA* 2007; 104: 9828–33.
- Feinberg TE, Venneri A, Simone AM, Fan Y, Northoff G. The neuroanatomy of asomatognosia and somatoparaphrenia. *J Neurol Neurosurg Psychiatry* 2010; 81: 276–81.
- Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–98.
- Forgiarini M, Gallucci M, Maravita A. Racism and the empathy for pain on our skin. *Front Psychol* 2011; 2: 108.
- Fotopoulou A, Jenkinson PM, Tsakiris M, Haggard P, Rudd A, Kopelman MD. Mirror-view reverses somatoparaphrenia: Dissociation between first- and third-person perspectives on body ownership. *Neuropsychologia* 2011; 49: 3946–55.
- Fowles DC, Christie MJ, Edelberg R, Grings WW, Lykken DT, Venables PH. Publication recommendations for electrodermal measurements. *Psychophysiology* 1981; 18: 232–39.
- Gallace A, Torta DM, Moseley GL, Iannetti GD. The analgesic effect of crossing the arms. *Pain* 2011; 152: 1418–23.
- Gandola M, Invernizzi P, Sedda A, Ferrè ER, Sterzi R, Sberna M, et al. An anatomical account of somatoparaphrenia. *Cortex* 2012; 48: 1165–78.
- Garbarini F, Rabuffetti M, Piedimonte A, Pia L, Ferrarin M, Frassinetti F, et al. 'Moving' a paralysed hand: bimanual coupling effect in patients with anosognosia for hemiplegia. *Brain* 2012; 135: 1486–97.
- Graziano MSA, Cooke DF. Parieto-frontal interactions, personal space, and defensive behavior. *Neuropsychologia* 2006; 44: 2621–35.
- Guterstam A, Petkova VI, Ehrsson HH. The illusion of owning a third arm. *PLoS One* 2011; 23, 6: e17208.
- Haggard P, Iannetti GD, Longo MR. Spatial sensory organization and body representation in pain perception. *Curr Biol* 2013; 23: R164–76.

- Halligan PW, Marshall JC, Wade DT. Unilateral somatoparaphrenia after right hemisphere stroke: a case description. *Cortex* 1995; 31: 173–82.
- Hediger H. Studies of the psychology and behavior of captive animals in zoos and circuses. Vancouver, CA: Criterion Books; 1955.
- Höfle M, Hauck M, Engel AK, Senkowski D. Viewing a needle pricking a hand that you perceive as yours enhances unpleasantness of pain. *Pain* 2012; 153: 1074–81.
- Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). *Exp Brain Res* 2010; 205: 1–12.
- Ijsselstein WA, de Kort YAW, Haans A. Is this my hand i see before me? The rubber hand illusion in reality, virtual reality, and mixed reality. *Presence-Teleop Virt* 2006; 15: 455–464.
- Invernizzi P, Gandola M, Romano D, Zapparoli L, Bottini G, Paulesu E. What is mine? Behavioral and anatomical dissociations between somatoparaphrenia and anosognosia for hemiplegia. *Behav Neurol* 2013; 26: 139–50.
- Ionta S, Heydrich L, Lenggenhager B, Mouthon M, Fornari E, Chapuis D, et al. Multisensory mechanisms in temporo-parietal cortex support self-location and first-person perspective. *Neuron* 2011; 70: 363–74.
- Jenkinson PM, Haggard P, Ferreira NC, Fotopoulou A. Body ownership and attention in the mirror: Insights from somatoparaphrenia and the rubber hand illusion. *Neuropsychologia* 2013; 51: 1453–62.
- Jensen J, McIntosh AR, Crawley AP, Mikulis DJ, Remington G, Kapur S. Direct activation of the ventral striatum in anticipation of aversive stimuli. *Neuron* 2003; 40: 1251–7.
- Lenggenhager B, Tadi T, Metzinger T, Blanke O. Video ergo sum: manipulating bodily self-consciousness. *Science* 2007; 317: 1095–9.
- Lenz FA, Casey KL, Jones EG, Willis WD. Organization of the central pain pathways. In: *The human pain system*. Cambridge: Cambridge University Press; 2010. p. 64–195.
- Levinson DF, Edelberg R. Scoring criteria for response latency and habituation in electrodermal research: a critique. *Psychophysiology* 1985; 22: 417–26.
- Longo MR, Betti V, Aglioti SM, Haggard P. Visually induced analgesia: seeing the body reduces pain. *J Neurosci* 2009; 29: 12125–30.
- Longo MR, Schüür F, Kammers MP, Tsakiris M, Haggard P. What is embodiment? A psychometric approach. *Cognition* 2008; 107: 978–98.
- Lykken DT, Venables PH. Direct measurement of skin conductance: a proposal for standardization. *Psychophysiology* 1971; 8: 656–72.
- Mancini F, Longo MR, Kammers MP, Haggard P. Visual distortion of body size modulates pain perception. *Psychol Sci* 2011; 22: 325–30.
- Masson MEJ, Loftus GR. Using confidence intervals for graphically based data interpretation. *Can J Exp Psychol* 2003; 57: 203–20.
- Medina J, Beauvais J, Datta A, Bikson M, Coslett HB, Hamilton RH. Transcranial direct current stimulation accelerates allocentric target detection. *Brain Stimul* 2013; 6: 433–9.
- Medina J, Coslett HB. From maps to form to space: Touch and the body schema. *Neuropsychologia* 2010; 48: 645–54.
- Mondini S, Mapelli D, Vestri A, Bisiacchi PS. *Esame Neuropsicologico Breve*. Milano: Raffaello Cortina Editore; 2003.
- Moseley GL, Olthof N, Venema A, Don S, Wijers M, Gallace A, et al. Psychologically induced cooling of a specific body part caused by the illusory ownership of an artificial counterpart. *Proc Natl Acad Sci USA* 2008; 105: 13169–73.
- Nightingale S. Somatoparaphrenia: a case report. *Cortex* 1982; 18: 463–7.
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971; 9: 97–113.
- Perez-Marcos D, Slater M, Sanchez-Vives MV. Inducing a virtual hand ownership illusion through a brain-computer interface. *Neuroreport* 2009; 20: 589–94.
- Petkova VI, Ehrsson HH. When right feels left: referral of touch and ownership between the hands. *PLoS One* 2009; 4: e6933.
- Pia L, Garbarini F, Fossataro C, Forna L, Berti A. Pain and body awareness: evidence from brain-damaged patients with delusional body ownership. *Front Hum Neurosci* 2013; 7: 298.
- Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, et al. Dissociating pain from its anticipation in the human brain. *Science* 1999; 284: 1979–81.
- Pugnaghi M, Molinari M, Panzetti P, Nichelli PF, Zamboni G. “My sister’s hand is in my bed”: a case of somatoparaphrenia. *Neurol Sci* 2012; 33: 1205–7.
- Rhudy JL, McCabe KM, Williams AE. Affective modulation of autonomic reactions to noxious stimuli. *Int J Psychophysiol* 2007; 63: 105–9.
- Rhudy JL, Williams AE, McCabe KM, Russell JL, Maynard LJ. Emotional control of nociceptive reactions (ECON): do affective valence and arousal play a role? *Pain* 2008; 136: 250–61.
- Rhudy JL, Bartley EJ, Williams AE. Habituation, sensitization, and emotional valence modulation of pain responses. *Pain* 2010; 148: 320–7.
- Rohde M, Di Luca M, Ernst MO. The rubber hand illusion: feeling of ownership and proprioceptive drift do not go hand in hand. *PLoS One* 2011; 6: e21659.
- Romano D, Bottini G, Maravita A. Perceptual effects of the mirror box training in normal subjects. *Restor Neurol Neurosci* 2013; 31: 373–86.
- Rorden C, Brett M. Stereotaxic display of brain lesions. *Behav Neurol* 2000; 12: 191–200.
- Rorden C, Karnath HO. Using human brain lesions to infer function: a relic from a past era in the fMRI age? *Nat Rev Neurosci* 2004; 5: 813–19.
- Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. *J Cogn Neurosci* 2007; 19: 1081–1088.
- Spinazzola L, Pia L, Folegatti A, Marchetti C, Berti A. Modular structure of awareness for sensorimotor disorders: evidence from anosognosia for hemiplegia and anosognosia for hemianaesthesia. *Neuropsychologia* 2008; 46: 915–26.
- Sterzi R, Bottini G, Celani MG, Righetti E, Lamassa M, Ricci S, et al. Hemianopia, hemianaesthesia, and hemiplegia after right and left hemisphere damage. A hemispheric difference. *J Neurol Neurosurg Psychiatry* 1993; 56: 308–10.
- Tsakiris M. My body in the brain: a neurocognitive model of body-ownership. *Neuropsychologia* 2010; 48: 703–12.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002; 15: 273–89.
- Vallar G, Bottini G, Sterzi R, Passerini D, Rusconi ML. Hemianesthesia, sensory neglect, and defective access to conscious experience. *Neurology* 1991; 41: 650–2.
- Vallar G, Bottini G, Sterzi R. Anosognosia for left-sided motor and sensory deficits, motor neglect, and sensory hemi-inattention: is there a relationship? *Prog Brain Res* 2003; 142: 289–301.
- Vallar G, Ronchi R. Somatoparaphrenia: a body delusion. A review of the neuropsychological literature. *Exp Brain Res* 2009; 192: 533–51.
- van Stralen HE, van Zandvoort MJE, Dijkerman HC. The role of self-touch in somatosensory and body representation disorders after stroke. *Phil Trans R Soc B* 2011; 366: 3142–3152.
- Vocat R, Saj A, Vuilleumier P. The riddle of anosognosia: does unawareness of hemiplegia involve a failure to update beliefs? *Cortex* 2013; 49: 1771–81.
- Vuilleumier P. Anosognosia: the neurology of beliefs and uncertainties. *Cortex* 2004; 40: 9–17.
- Williams AE, Rhudy JL. Emotional modulation of autonomic responses to painful trigeminal stimulation. *Int J Psychophysiol* 2009; 71: 242–7.
- World Medical Organization. Declaration of Helsinki. *Br Med J* 1996; 313: 1448–49.
- Zeller D, Gross C, Bartsch A, Johansen-Berg H, Classen J. Ventral premotor cortex may be required for dynamic changes in the feeling of limb ownership: a lesion study. *J Neurosci* 2011; 31: 4852–7.