

The desire for healthy limb amputation: structural brain correlates and clinical features of xenomelia

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Xenomelia is the oppressive feeling that one or more limbs of one's body do not belong to one's self. We present the results of a thorough examination of the characteristics of the disorder in 15 males with a strong desire for amputation of one or both legs. The feeling of estrangement had been present since early childhood and was limited to a precisely demarcated part of the leg in all individuals. Neurological status examination and neuropsychological testing were normal in all participants, and psychiatric evaluation ruled out the presence of a psychotic disorder. In 13 individuals and in 13 pair-matched control participants, magnetic resonance imaging was performed, and surface-based morphometry revealed significant group differences in cortical architecture. In the right hemisphere, participants with xenomelia showed reduced cortical thickness in the superior parietal lobule and reduced cortical surface area in the primary and secondary somatosensory cortices, in the inferior parietal lobule, as well as in the anterior insular cortex. A cluster of increased thickness was located in the central sulcus. In the left hemisphere, affected individuals evinced a larger cortical surface area in the inferior parietal lobule and secondary somatosensory cortex. Although of modest size, these structural correlates of xenomelia appear meaningful when discussed against the background of some key clinical features of the disorder. Thus, the predominantly right-sided cortical abnormalities are in line with a strong bias for left-sided limbs as the target of the amputation desire, evident both in our sample and in previously described populations with xenomelia. We also propose that the higher incidence of lower compared with upper limbs (~80% according to previous investigations) may explain the erotic connotations typically associated with xenomelia, also in the present sample. These may have their roots in the proximity of primary somatosensory cortex for leg representation, whose surface area was reduced in the participants with xenomelia, with that of the genitals. Alternatively, the spatial adjacency of secondary somatosensory cortex for leg representation and the anterior insula, the latter known to mediate sexual arousal beyond that induced by direct tactile stimulation of the genital area, might play a role. Although the right hemisphere regions of

significant neuroarchitectural correlates of xenomelia are part of a network reportedly subserving body ownership, it remains unclear whether the structural alterations are the cause or rather the consequence of the long-standing and pervasive mismatch between body and self.

Keywords: body ownership; identity disorders; parietal lobe; insula; surface-based morphometry

Abbreviations: SI = primary somatosensory cortex; SII = secondary somatosensory cortex

Introduction

Current investigations of how the human brain mediates the experience of the body is either directed to changes in corporeal awareness after brain damage or focused on the study of bodily illusions induced in healthy persons. Neurological patients evince a remarkable range of anomalies in bodily experience (Critchley, 1953; Hécaen and de Ajuriaguerra, 1952; de Vignemont, 2010). The body, or frequently only one lateral half, may seem absent as in (hemi)asomatognosia (von Stockert, 1934; Feinberg *et al.*, 2010), belong to another person as in somatoparaphrenia (Gerstmann, 1942; Vallar and Ronchi, 2009), display a will of its own as in alien limb syndrome (Marchetti and Della Sala, 1998) or form the target of abusive and self-destructive behaviour as in misoplegia (Critchley, 1974; Loetscher *et al.*, 2006). In some instances, a ghostly companion is perceived as following the person's every move (Brugger *et al.*, 1996), or one's body and self are experienced as duplicated (Brugger *et al.*, 1997) or spatially disconnected (Blanke *et al.*, 2004). In all these conditions, the right parietal cortex plays a prominent role. Damage to the inferior parietal lobule typically leads to neglect of body space (Committeri *et al.*, 2007) and derangements in corporeal awareness such as anorexia nervosa (Pietrini *et al.*, 2011) and asymbolia for pain (Berthier *et al.*, 1988). Aspects of the superior parietal lobule form a convergence zone of somatosensory, visual and vestibular signals, and are critical for sensorimotor integration (Wolpert *et al.*, 1998). This binding of sensory information with motor intention and action is at the heart of a unified sense of the body in space (Tsakiris, 2010). It is also a prerequisite for the 'animation' of a body part, that is, its acceptance, beyond the appreciation of bare ownership, as something familiar and dear (Hilti and Brugger, 2010).

Work in healthy human subjects underlines the importance of both inferior parietal lobule and superior parietal lobule in mediating body ownership (Kammers *et al.*, 2009) and the integrative mental imagery of limb configurations (Wolbers *et al.*, 2003). Especially the right superior parietal lobule was implicated in monitoring the illusory displacement of a limb, irrespective of its laterality (Naito *et al.*, 2005). Furthermore, both primary and secondary areas of hand representation are involved in mediating the rubber hand illusion, where touch to one's hand experienced simultaneously with the visual observation of a rubber hand being touched, leads to the feeling of an incorporation of the dummy hand (e.g. Tsakiris *et al.*, 2007) and a diminished animation of the real hand (Moseley *et al.*, 2008).

In addition to the parietal lobes, the insular cortex is crucially involved in establishing and maintaining the sense of body ownership and the monitoring of the homeostatic state of the body (Craig, 2003, 2011; Critchley *et al.*, 2004). Again, evidence from both patient studies and experiments with neurologically healthy participants supports the predominant involvement of the right-sided insula in mediating interoceptive awareness (Critchley *et al.*, 2004; Karnath *et al.*, 2005; Craig, 2009; Karnath and Baier, 2010).

There is one particular aberration in the experience of one's body that is reported by neurologically and psychiatrically healthy persons and yet not dependent on any of the illusion techniques known to induce a transiently altered corporeal awareness. It is the continuous experience of being 'overcomplete' in possessing four limbs and the resulting request for surgical removal of the unwanted 'foreign' extremity. Recently labelled xenomelia ('foreign limb' syndrome; McGeoch *et al.*, 2011), the condition was previously termed body integrity identity disorder (First, 2005; First and Fisher, 2012) to emphasize its nosological relatedness to other forms of a mismatch between body and self, especially gender identity disorder (Lawrence, 2006). Relatively large-scale surveys and interview studies (First, 2005, $n = 52$; Blanke *et al.*, 2009, $n = 20$; Johnson *et al.*, 2011, $n = 97$) agree that most subjects with xenomelia are male (90, 85 and 84%, respectively, in the three aforementioned references); the majority desires a leg amputation (73, 80 and 81%, respectively), and the ratio of left- to right-sided target limbs clearly favours the former (55% to 27%, 60% to 20% and 42% to 28%, respectively). A considerable minority of persons with xenomelia desire a bilateral amputation (18, 20 and 30%, respectively), a figure that is probably even higher among affected females (Giummarra *et al.*, 2012). While earlier conceptualizations of xenomelia as a sexual paraphilia (Money *et al.*, 1977) or an erotically motivated urge for amputation (Sue, 1785) appear outdated, we and others have proposed that the condition may be due to an under-representation of the target limb in the right parietal cortex (Hilti and Brugger, 2010; Brang *et al.*, 2008). Recent data support this assumption. McGeoch *et al.* (2011) investigated four subjects desiring the amputation of one (two right, one left) or both legs. Specifically, they applied tactile stimulation to sites above and below the desired amputation line during magnetoencephalography recordings. Four control persons without xenomelia were subject to the same procedure. Reduced touch-related activation was found in the right superior parietal lobule for the xenomelic participants' affected legs, despite the fact that two subjects wanted to have their right leg removed. McGeoch *et al.* (2011) concluded that in accordance with the clinical and experimental literature cited earlier in the text,

the superior parietal lobule of the right hemisphere is crucial for the representation of the human body as a whole. McGeoch *et al.* (2011) argued that a mismatch between the lack of a higher-order representation of a limb and spared lower-level sensory functions might be at the heart of xenomelia. In a previous communication, the same authors presented indirect evidence that the feeling of a limb as 'foreign' may also be linked to a dysfunctional insular cortex (Brang *et al.*, 2008).

This study set out to investigate structural brain correlates of xenomelia with the use of MRI. We analysed cortical thickness and surface area in subjects with xenomelia and a carefully matched control group, and predicted grey matter differences in the right superior parietal lobule (McGeoch *et al.*, 2011) and the right insula (Brang *et al.*, 2008).

Based on work in healthy subjects' altered limb ownership in the rubber hand illusion, we also expected alterations in the right inferior parietal lobule (Lloyd *et al.*, 2006; Kammers *et al.*, 2009) and primary (SI) and secondary somatosensory (SII) cortices (Schaefer *et al.*, 2006; Tsakiris *et al.*, 2007). A role of SI and SII in xenomelia is also suggested by low-level somatosensory differences (e.g. paraesthesias) in the phenomenal experience of the non-accepted compared with the corresponding accepted limb in some subjects with the disorder (Blanke *et al.*, 2009; Johnson *et al.*, 2011). Premotor cortex, although typically involved in the rubber hand illusion, was not regarded as a region of interest in connection with xenomelia, as its activation specifically reflects the incorporation component of the fake hand (Ehrsson *et al.*, 2004), which is present in the illusion context but obviously absent in the clinical context of an amputation desire.

Materials and methods

Subjects

Fifteen males with xenomelia were recruited from an internet site (<http://www.biid-dach.org/>) and invited to take part in a behavioural and neuroimaging study of the condition (Hilti, 2012). Two participants did not meet the inclusion criteria for MRI scanning (one had a metallic splinter in one of his eyes and the other was too obese to fit into the scanner). Of the 13 remaining participants (see Table 1 for subject characteristics), all desired an above-knee amputation: eight of the left leg, two of the right leg and three a bilateral leg amputation (one of them with a clear asymmetry in favour of keeping the right leg). Participants' age ranged from 28–73 years [mean = 49.3 years, standard deviation (SD) = 14.5 years], and their years of education ranged from 12 to 20 years (mean = 15.4 years, SD = 3.0 years). Twelve of the participants with xenomelia were both right-handed and right-footed, the remaining participant (Case 9) showed a left-side preference for both hand and foot (Coren, 1993). Scores on the Zurich Xenomelia Scale (Aoyama *et al.*, 2012), including its three subscores (i) for the strength of the amputation desire; (ii) the erotic attraction by amputees and (iii) the extent to which a participant goes to pretend being amputated, are also listed in Table 1.

Thirteen males served as control subjects. They were pair-wise matched to the participants with xenomelia with respect to hand and foot preference, age [range 34–73 years; mean = 50.2 years, SD = 12.5 years; paired *t*-test: $t(12) = -0.82$, $P = 0.42$] and education

[range 12–20 years; mean = 14.8 years, SD = 2.8 years; paired *t*-test: $t(12) = 1.58$, $P = 0.14$].

All participants gave written informed consent to take part in the study, which was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Hospital Zurich. All reported an uneventful medical history without any known complications during pregnancy and a normal child development. Neurological status examination and extensive neuropsychological evaluations proved to be normal in all participants (Hilti, 2012). Psychiatric assessment comprised a 2-h structured clinical interview (Wittchen and Frydreich, 1997) and the administration of various self-rating scales to measure schizotypal, obsessive-compulsive and dissociative personality traits, among others.

Magnetic resonance imaging data acquisition

Structural MRI scans were acquired using a 3.0-T Philips Achieva whole-body scanner (Philips Medical Systems) equipped with a transmit/receive body coil and an eight-element head coil. A volumetric 3D T₁-weighted fast field echo sequence was applied twice to obtain two scans each with a duration of 468 s and a spatial resolution of $0.94 \times 0.94 \times 1.0 \text{ mm}^3$ (acquisition matrix: 256×256 pixels, 160 slices). Further imaging parameters were field of view = $240 \times 240 \text{ mm}^2$, echo time = 3.7 ms, repetition time = 8.06 ms, flip angle = 8° and sensitivity encoding factor = 2.1. The two scans were then co-registered and averaged to increase the contrast-to-noise ratio. Diffusion tensor imaging and resting state functional MRI scans were acquired in addition. The results of the diffusion tensor imaging and resting state functional MRI analyses will be reported elsewhere.

Surface-based morphometry

Cortical surface reconstruction was performed with the Freesurfer image analysis suite, which is documented and freely available online (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in previous publications (Dale *et al.*, 1999; Fischl *et al.*, 1999a, b; Fischl and Dale, 2000). Briefly, this processing includes removal of non-brain tissue, automated Talairach transformation, segmentation of subcortical white matter, intensity normalization, tessellation of the grey/white matter boundary, automated topology correction and surface deformation. Once the cortical models have been completed, a number of deformable procedures were performed, including surface inflation, registration to a spherical atlas to match cortical geometry across subjects and parcellation of the cerebral cortex. This method uses both intensity and continuity information from the entire 3D MRI volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the grey/white boundary to the grey matter/CSF boundary at each vertex on the tessellated surface. The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. They are not restricted to the voxel resolution of the original data and are thus capable of detecting sub-millimetre differences in cortical thickness between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas *et al.*, 2002) and manual measurements (Kuperberg *et al.*, 2003; Salat *et al.*, 2004). Accuracy of Freesurfer's automatically generated grey and white matter boundaries was checked by a skilled observer (J.H.), and no manual corrections were necessary. Cortical thickness and surface area maps were resampled for all subjects into

Table 1 Characteristics of the participants with xenomelia

Participant	Age (years)	Target leg (s)	Approximate height of desired amputation	Amputation desires since age (years)	Triggering event ^b	Mean scores ^a on Zurich Xenomelia Scale (SD)			
						Subscale 'amputation desire'	Subscale 'erotic attraction'	Subscale 'pretending behaviour'	Total scale score
1	41	Left	10 cm above knee ^c	8–10	None	5.8 (0.5)	4.3 (2.4)	3.8 (2.6)	4.6 (1.7)
2	46	Left	Middle of thigh	'Since I can remember' ^d	(Various encounters with amputees)	4.0 (1.8)	5.3 (1.5)	4.3 (1.5)	4.5 (0.2)
3	63	Left	At upper third of thigh	7	Admiration for male leg amputee	5.5 (1.0)	2.5 (1.0)	4.0 (2.5)	4.0 (0.8)
4	57	Left	Middle of thigh	6–8	Various encounters with amputees	5.5 (1.0)	3.8 (1.5)	3.8 (2.2)	4.3 (0.6)
5	29	Left	Middle of thigh	4–5	None	5.0 (1.4)	6.0 (0.0)	4.3 (2.2)	5.1 (1.1)
6	28	Left	15 cm below hip joint	7	Contact with male leg amputee and female arm amputee	5.5 (1.0)	6.0 (0.0)	4.8 (2.5)	5.4 (1.3)
7	44	Left	15 cm below hip joint	9	None	5.8 (0.5)	3.3 (1.0)	4.0 (2.2)	4.3 (0.9)
8	67	Left	10 cm above knee	8	Postman was an arm amputee	5.5 (0.6)	5.8 (0.5)	3.8 (2.6)	5.0 (1.2)
9	33	Right	25 cm above knee	8–10	(Contact with male leg amputee)	5.5 (1.0)	4.3 (1.0)	1.8 (1.0)	3.8 (1.8)
10	56	Right	Within upper third of thigh ^e	10	Various encounters with amputees	4.3 (1.5)	4.5 (0.6)	1.8 (0.5)	3.5 (0.6)
11	45	Both	At upper third of thigh	9	None	5.8 (0.5)	5.0 (0.8)	4.0 (2.2)	4.9 (0.9)
12	73	Both ^f	5 cm above knee	'Since I can remember'	(Contact with male leg amputee)	4.8 (1.5)	6.0 (0.0)	3.5 (1.7)	4.8 (0.9)
13	59	Both	15 cm above knee	7	(Various encounters with amputees)	5.5 (1.0)	5.0 (2.0)	4.5 (2.4)	5.0 (0.7)

a Minimum = 1, maximum = 6.

b If in brackets, events were only considered (and not claimed) to be causally related to the amputation desire.

c 'Rational decision' in view of prosthesis fitting; otherwise desires exarticulation.

d Proceeded to amputation ~1 year after study completion.

e Blurred line of desired amputation.

f Amputation desire markedly pronounced for left leg.

a common spherical coordinate system. The data were then smoothed on the surface tessellation using an iterative nearest-neighbour averaging procedure with 166 iterations, equivalent to applying a 2D Gaussian smoothing kernel along the cortical surface with a full-width at half-maximum of ~15 mm.

Statistical analyses

Group comparison

We computed vertex-wise analyses in the parietal lobe and insula bilaterally to find local differences in cortical thickness and surface area between participants with xenomelia and control participants. To examine differences between the two groups and in face of our specific and strong *a priori* hypotheses, we used independent sample *t*-tests with a height threshold of $P < 0.01$ (uncorrected for multiple comparisons) and a cluster extent threshold of $k > 25 \text{ mm}^2$ that adequately helps protecting against spurious findings because false-positive results do not cluster in space (Forman *et al.*, 1995; Lieberman and Cunningham, 2009). In addition, we also applied correction for multiple comparisons using Monte Carlo simulations on the cluster extent as implemented in the Freesurfer software.

Correlations

We correlated individual strength of the amputation desire with the averaged cortical thickness and surface area values within the clusters found in the group comparisons. Because these values are not entirely independent from the group comparisons, we also calculated the analogous correlations vertex-wise across parietal and insular regions. Clusters were height-thresholded at $P < 0.01$ (uncorrected for multiple comparisons), with a cluster extent threshold of $k > 24 \text{ mm}^2$. The right hemisphere regions subjected to the statistical analyses are shown in the Supplementary Fig. 1.

Results

Psychiatric assessment

The structured clinical interview did not produce evidence for a psychotic disorder in any of the participants with xenomelia. Four participants were diagnosed with mood disorder (three lifetime major depressive and one current major depressive), with depressive symptoms that were, however, without exception ascribed to the state of xenomelia. The results of the self-rating scales are presented in Supplementary Table 1. Unpaired *t*-tests ($df = 24$) did not reveal differences between participants with xenomelia and control participants with respect to body dysmorphic or obsessive-compulsive disorder, schizotypal personality, depression and anxiety, and measures related to gender and sex roles. Participants with xenomelia tended to be more impulsive ($P = 0.07$), and to score higher on inventories assessing borderline symptoms ($P = 0.07$) and dissociative symptoms ($P = 0.08$). These tendencies were, however, inflated by items specifically asking for the rater's dissatisfaction with the own body or parts of it, and they disappeared after these specific items were removed ($P > 0.1$; Supplementary Table 1). Paired *t*-tests ($df = 12$), suggested by peer review, did not change this pattern of results.

Global brain measurements

Intracranial volume did not significantly differ between groups. Neither left nor right hemispheric differences in cortical white matter volume, subcortical grey matter volume and cortical surface area, thickness and volume were found between the two groups (Supplementary Table 2).

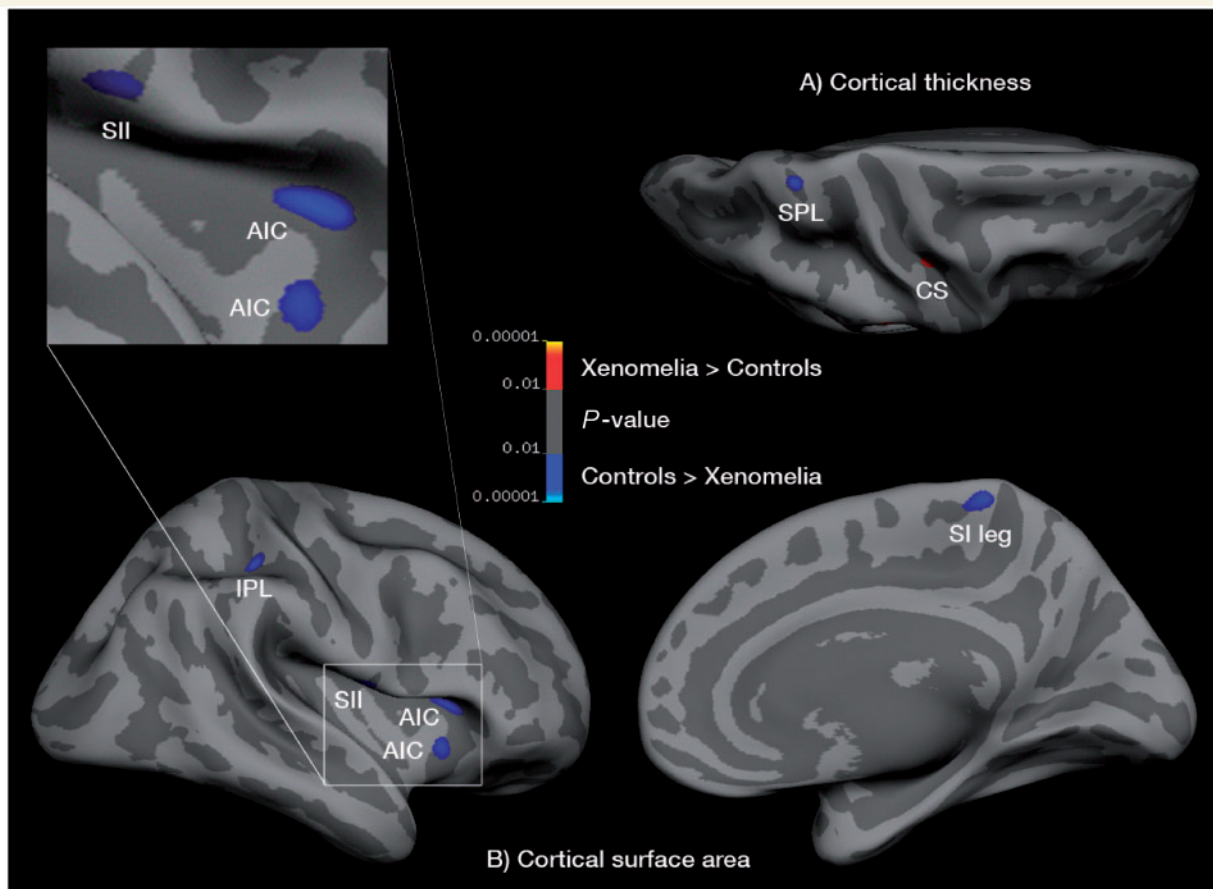


Figure 1 Altered right hemispheric neuroarchitecture in participants with xenomelia compared with control participants. Cortical thickness (A) is decreased (blue–light blue) in the superior parietal lobule (SPL) and increased (red–yellow) in the central sulcus (CS) in participants with xenomelia compared with control participants. Cortical surface area (B) is decreased in the anterior insular cortex (AIC), primary somatosensory leg representation (SI leg), secondary somatosensory cortex (SII) and in the inferior parietal lobule (IPL) of participants with xenomelia. The magnified inset is tilted by 30° to show the entire extent of the SII cluster. Further information is given in Table 2. The statistical parametric maps are overlaid on the mean right hemispheric inflated surface model of the 26 participants under investigation.

Table 2 Altered right hemispheric neuroarchitecture in participants with xenomelia compared with control participants

Measure and anatomical location	Cluster size (mm ²)	Number of vertices	MNI coordinates			t-value df = 24	P-value	Effect size (d)
			x	y	z			
Cortical thickness								
Superior parietal lobule (SPL, Fig. 1A)	58.2	115	17	−50	61	3.64	0.0013	1.49
Inferior parietal lobule (IPL, not shown) ^a	90.3	220	57	−27	38	−3.34	0.0027	1.37
Central sulcus (CS, Fig. 1A) ^a	58.5	125	33	−16	40	−3.06	0.0054	1.25
Cortical surface area								
Anterior insular cortex (AIC, Fig. 1B, upper cluster)	86.9	207	32	25	9	4.03	0.0005	1.65
Anterior insular cortex (AIC, Fig. 1B, lower cluster)	44.7	109	32	20	−4	3.23	0.0035	1.32
Primary somatosensory cortex (SI leg, Fig. 1B)	62.8	167	5	−38	62	3.37	0.0025	1.38
Secondary somatosensory cortex (SII, Fig. 1B)	51.5	108	54	−3	9	3.22	0.0037	1.31
Inferior parietal lobule (IPL, Fig. 1B)	63.5	158	35	−31	42	4.02	0.0005	1.64

Effect size was computed according to the formula by Cohen. Clusters were height thresholded at $P < 0.01$ (uncorrected for multiple comparisons), with a cluster extent threshold of $k > 25$ mm².

^a These measures were increased in participants with xenomelia. All other measures were reduced compared with control participants.

Local brain measurements

Group differences in cortical morphology were evident in several regions within the right parietal lobe and the right anterior insula (Fig. 1 and Table 2).

In the right superior parietal lobule, a cluster with significantly reduced cortical thickness was found for the group of subjects with xenomelia compared with the control subjects [Fig. 1A; Montreal Neurological Institute (MNI) coordinates of peak: $x = 17$, $y = -50$, $z = 61$]. In two other clusters, one located in the right inferior parietal lobule (not shown; MNI coordinates of peak: $x = 57$, $y = -27$, $z = 38$) and the other located in the right central sulcus in the vicinity of the region where the left hand is represented (Fig. 1A, MNI coordinates of peak: $x = 33$, $y = -16$, $z = 40$), increased cortical thickness was found in participants with xenomelia compared with control subjects.

Cortical surface area in subjects with xenomelia was also reduced in a cluster in the right inferior parietal lobule (Fig. 1B; MNI coordinates of peak: $x = 35$, $y = -31$, $z = 42$).

On the medial side of the right parietal lobe, a cluster with significantly reduced cortical surface area for the xenomelia group was obtained (Fig. 1B; MNI coordinates of peak: $x = 5$, $y = -38$, $z = 62$), coinciding with the known location of the primary somatosensory representation of the left leg (*cf.* functional MRI peak activation after stimulation of the left hallux in Kell *et al.*, 2005, Talairach coordinates: $x = 12$, $y = -39$, $z = 72$). Furthermore, a cluster within the upper bank of the right lateral sulcus also showed a reduced surface area in participants with xenomelia. This region is part of the parietal operculum and comprises SII of foot representation, *i.e.* Brodmann area 43 (Ruben *et al.*, 2001). The MNI coordinates of peak ($x = 54$, $y = -3$, $z = 9$) were similar to the SII peak activation coordinates found for leg stimulation in a functional MRI study by Eickhoff *et al.* (2007) (Talairach coordinates $x = 57$, $y = 4$, $z = 11$). Finally, in the right anterior insular cortex/frontal operculum, two clusters with reduced cortical surface area were found in subjects with xenomelia compared with control subjects (Fig. 1B; MNI coordinates of peak: $x = 32$, $y = 25$, $z = 9$ and $x = 32$, $y = 20$, $z = -4$).

Although xenomelia has been postulated as a specifically right parietal syndrome, we also investigated the left hemisphere for reasons of completeness. Differences between the two participant groups in left hemisphere grey matter architecture (analysed regions homologous to those depicted in Supplementary Fig. 1) are listed in Supplementary Table 3 and illustrated in Supplementary Fig. 2. There were clusters of increased cortical surface area in xenomelic participants' left inferior parietal lobule and left secondary somatosensory cortex. No left hemispheric group differences were found with respect to cortical thickness.

Post hoc correlations between the strength of an individual's amputation desire as measured by the primary subscore of the Zurich Xenomelia Scale (raw scores in Table 1) and the morphometric variables averaged within regions of significant group differences revealed a significant negative correlation with the surface area of the right inferior parietal lobule cluster depicted in Fig. 1B (Pearson $r = -0.67$, two-tailed $P < 0.02$; Fig. 2). As pointed out by peer review, this correlation analysis is not entirely independent of the group comparison reported earlier in the text,

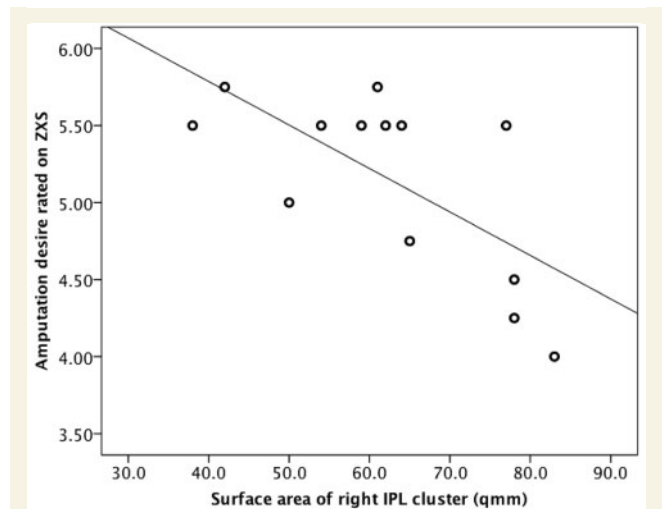


Figure 2 Correlation between amputation desire and neuroarchitectural features. Mean scores on the subscale 'amputation desire' of the Zurich Xenomelia Scale (ZXS, possible scores from 1 to 6) are negatively associated with the surface area of a cluster in the right inferior parietal lobule (IPL) (Pearson's $r = -0.67$, $P < 0.02$, two-tailed).

as the primary subscore of the Zurich Xenomelia Scale, if collected in the control participants, would also binarize the two groups. This would inflate the Pearson's correlation coefficient, which must therefore be interpreted with caution. Nevertheless, we point out that the structural features of the right inferior parietal lobule cluster are related to the clinical features of the amputation desire in a specific way; notably, the subscores of the Zurich Xenomelia Scale reflecting the strength of erotic attraction by amputees and that of the frequency of pretending to be an amputee were uncorrelated to this neuroarchitectural parameter ($P > 0.38$ and $P > 0.33$, respectively).

In addition to the correlation based on the clusters found in the group comparisons (Fig. 2), we also regressed the xenomelic participants' primary subscore of the Zurich Xenomelia Scale against right hemispheric cortical thickness and surface area vertex-wise across parietal and insular regions. The strength of an individual's amputation desire was negatively correlated with cortical surface area in the right SII and in the right anterior insular cortex, two clusters located in close vicinity to those representing significant structural differences in the group comparison (Supplementary Fig. 3 and Supplementary Table 4).

Discussion

Xenomelia is not a disorder that can readily be 'localized' to any circumscribed region of the human brain. We have to assume that it reflects a breakdown in a network of key areas coding for different facets of the experience of 'owning' a body. Contemporary neuropsychiatry is unable to sketch precise working diagrams for the single components of body ownership, but in gross terms, the circuits possibly involved in the maintenance of the integrity between body and self have recently been outlined (Giummarra *et al.*, 2008; Longo *et al.*, 2010; Tsakiris, 2010; Moseley *et al.*,

2012). On the phenomenal level, these circuits mediate the feeling of being the agent of one's limb movements, the coherence across sensory inputs (e.g. visually observed touch of a body part matches the expected tactile sensation), the continuity in integrating online information about the state of the body (including proprioceptive, vestibular and interoceptive information) with some higher-order representation, 'schema' or 'image' of the human body, and finally the affective binding of body parts into an offline representation of one's body as a whole (a process we have dubbed 'animation'; Hilti and Brugger, 2010). Phenomenal reports of subjects suffering from xenomelia should form the starting point of any theorizing about how disruptions of these components (or of the interactions between them) explain the loss of ownership over a single body part (Giummarra *et al.*, 2011). For instance, subjects with xenomelia do not typically report the loss of agency over limb movements. Hence, any comparison of the disorder with the syndrome of the 'alien limb' does not appear warranted. We will discuss the potential significance of the structural correlates of xenomelia as revealed in the present study against the background of some clinical observations we consider key for the understanding of the disorder. To summarize, structural changes were found in the right superior parietal lobule and inferior parietal lobule, the right subcentral cortex comprising SII, the right paracentral lobule housing the primary somatosensory leg representation and the right anterior insular cortex. In the left hemisphere, an area within the inferior parietal lobule and the region corresponding to SII showed differences between participants with and without xenomelia.

Why are left-sided body parts primarily affected?

The neuroarchitectural differences between participants with and without xenomelia were strongly lateralized to the right cerebral hemisphere. This is in line with a recent magnetoencephalography study in four participants with xenomelia by McGeoch *et al.* (2011). Despite the fact that two of the four participants wanted to have their right leg removed, the authors found deficient right parietal signal processing after the application of touch to the undesired compared with the accepted body parts. This obvious asymmetry is compatible with the established wisdom that, unlike the left hemisphere, the right hemisphere supports a bilateral representation of one's body (Sterzi *et al.*, 1993; Vallar, 2007) and surrounding space (Stein, 1989). Consequently, hemispatial neglect, anosognosia for hemiplegia, hemiasomatognosia, supernumerary phantom limbs and the delusional disownership of one-half of the body all target the left side of body and space more frequently than the right. Lesions in the left hemisphere need to be much larger to produce right-sided symptoms of comparable severity and endurance because of the spared right hemispheric processing of right-sided stimuli (Joseph, 1988). In healthy research participants, this 'bilateral effect', characteristic of the right hemisphere, was demonstrated for both touch (Desmedt, 1977) and kinaesthesia (Naito *et al.*, 2005). Together with a more general specialization of the right hemisphere for self-related information (van Lancker, 1991; Keenan *et al.*, 2001), this

bilaterality effect may be at the heart of the limitation of the functional abnormalities (McGeoch *et al.*, 2011) and the structural findings reported here to the right cerebral hemisphere. It may also account for the biased desire for amputation of the left-sided limbs.

Why are legs primarily affected?

All of our participants with xenomelia longed for a leg amputation. In the larger population of affected individuals, the lower extremities are four times more likely to be the target of the amputation desire than the upper extremities (e.g. Blanke *et al.*, 2009; Johnson *et al.*, 2011). Taking up speculations by Ramachandran and Blakeslee (1998; p. 36) about the neural basis of foot fetishism, we here suggest that this bias may originate in the topographic particularities of the sensory homunculus in the post-central gyrus (and in its higher-integrative equivalents). Although empirical evidence is lacking, the consistent neighbouring of (i) arm/hand and face areas and (ii) the regions of leg/foot and genital representation is arguably the consequence of concurrent stimulation of hand and face and feet and genitals during foetal life (Farah, 1998). Indeed, tactile stimulation of the face leads to a referral of sensation to the phantom limb in arm amputees, whereas genital stimulation is typically referred to the phantom leg in lower-limb amputees (Henderson and Smyth, 1948). Likewise, the functional association of erotic arousal, either by thoughts about own-body amputations or by the sight of amputees, may be more than a mere coincidence. As evidenced by the subscores on the Zurich Xenomelia Scale, erotic/sexual arousal played a rather prominent role for our participants; in six of them, scores on the erotic subscale were higher than those on the subscore for mere amputation desire (Table 1). With respect to interconnections between somaesthesia and sexual arousal, the right insula might constitute a core region. There is a gradient of information integration along a posterior–anterior axis within the insula, with the caudal granular parts being considered a somatosensory association area (Mesulam and Mufson, 1985; Stephani *et al.*, 2011) and the more anterior agranular parts an area coding for the affective valence of bodily stimulation (Craig, 2009). For instance, tactile stimulation of the penis leads to posterior insula activation (Georgiadis and Holstege, 2005), whereas penile erection elicited by visual stimulus material activates portions of the anterior insular cortex (Moulier *et al.*, 2006). The insula's spatial adjacency to the SII for leg representation on the upper bank of the Sylvian fissure is thus not only compatible with the general view that 'the insula supports an integration of body and mind' (Jones *et al.*, 2010, p. 616), but may also place special emphasis on the integration of specifically lower limb representation and sexuality. A smaller, not larger, anterior insular surface area in the participants with xenomelia does not invalidate this speculation; a smaller cortical extension, whether regarding area, thickness or volume, does not necessarily translate into hypofunction. In fact, the literature on structural correlates of both above and below average neuropsychological performance is replete with relevant examples. For instance, professional ballet dancers with extraordinary somatosensory and motor skills showed decreased grey matter volumes in the sensorimotor network when compared

with non-dancers (Hänggi *et al.*, 2010). Conversely, individuals with amusia had increased cortical thickness in the auditory cortex compared with individuals with normal musical abilities (Hyde *et al.*, 2007).

What triggers xenomelia? A speculation

Introspective report indicates that about half of subjects with xenomelia consider an early childhood experience as causally related to their desire of amputation (Brugger, 2011; 9 of the 13 participants of the present study, *cf.* Table 1). Any account of early childhood memories should be treated with extreme caution, as the claimed 'memories' could also be later rationalizations (Gallo, 2010). However, the possibility remains that a hyperempathic response may constitute at least a correlate of the disorder. A considerable minority of healthy individuals report that seeing another person being touched elicits a sensation of touch on their own bodies (Banissy *et al.*, 2009; Fitzgibbon *et al.*, 2012 for review). Although in subjects with intact limbs this 'mirror-touch synaesthesia' is somatotopically correspondent (Banissy and Ward, 2007; Serino *et al.*, 2008), amputees commonly refer observed touch, irrespective of its observed location, to the phantom limb. This indicates that cross-modal referral of touch loses its topical specificity in reorganized body maps (e.g. Giummarra *et al.*, 2010; Goller *et al.*, in press). An atypical connectivity within parieto-insular circuits that code for both the visual observation of bodies and feelings originating within one's body was recently proposed and empirical evidence was presented for a 'hyperempathic' response in persons with mirror-touch synaesthesia (Banissy and Ward, 2007; Goller *et al.*, in press), arguably resting on such atypical connectivity. It is entirely speculative to assume that a hyperempathic response to the sight of an amputee could predispose the development of xenomelia. We emphasize, however, that this assumption is readily testable; mirror-touch synaesthesia should be higher in those subjects with xenomelia who ascribe their amputation desire to the repeated visual exposure to amputees' bodies. Given the interactions between an observer's own body form and his or her visual processing of the human body as reviewed by Corradi-Dell'Acqua and Tessari (2010), this possibility may not seem too far-fetched.

A network subserving body ownership

Recently, the concept of 'body matrix' was introduced to capture functional features of multisensory processing relevant to corporeal awareness, which were not included in older concepts of 'body schema' and 'body image' (Moseley *et al.*, 2012). In particular, the body matrix also includes representations of peripersonal space and respects the importance of homeostatic functions for the feeling of ownership over single body parts and the body as a whole. Neuroanatomically, it comprises, apart from SI and SII, regions of the posterior parietal cortex, including the inferior and superior parietal lobule and the insula with its connections to the brainstem. With the exception of the latter (and premotor cortex, also part of the matrix), these are exactly the regions in which surface-based morphology revealed significant differences between our two participant groups. Specifically, we found a thinner

cortical area in the right superior parietal lobule in participants with xenomelia compared with control participants. The location of this area is virtually identical to that described by McGeoch *et al.* (2011) as unresponsive to touch to the non-accepted body part in a magnetoencephalography study with four persons with xenomelia. These authors argued that the failure to activate the right superior parietal lobule reflected an insufficient sensorimotor integration of the particular limb. Specifically, a disintegration of seeing and feeling one's affected leg (both sensory qualities being spared in isolation) would lead to its being experienced as foreign. In fact, the role of the superior parietal lobule in 'binding' visual, somatosensory and motor signals about a limb is known from clinical cases. A breakdown of this integrative function was described by Wolpert *et al.* (1998) in a patient with a lesion to the (left) superior parietal lobule. This patient's right arm and leg would 'fade away' from awareness as soon as visual fixation of the limbs ceased or as long as movement was not consciously initiated. It seems as if the superior parietal lobule is optimally placed to house a multisensory-motor representation of one's body, as it receives inputs from SI, SII, (pre)motor cortex and the dorsal visual stream (Felleman and van Essen, 1991). Sudden acquired damage to this part of the brain leads to the often delusional conviction that one-half of one's body is absent or belongs to another person (Vallar and Ronchi, 2009; Feinberg *et al.*, 2010). In contrast, xenomelia has been viewed as an early developmental disorder of superior parietal lobule functioning, possibly even pointing to an innate component of body image (McGeoch *et al.*, 2011). We have previously suggested that the xenomelic person's 'incarnation without animation' is mirrored in the congenital amputee's 'animation without incarnation', i.e. the presence of phantom sensations in a limb missing since birth (Brugger *et al.*, 2000; Hilti and Brugger, 2010). Incidentally, in a female born without arms and legs, functional MRI parietal peak activations of unilateral phantom finger movements were restricted to the (bilateral) superior parietal lobule (Brugger *et al.*, 2000, Fig. 3).

Participants with xenomelia showed a reduced cortical surface area in a cluster located in the right inferior parietal lobule, and a xenomelic individual's rated magnitude of his amputation desire was negatively correlated with the size of this area. In many disturbances of a unified sense of bodily self, the inferior aspects of the parietal lobes are affected. Examples comprise personal (but not extrapersonal) neglect (Committeri *et al.*, 2007), anorexia nervosa (Pietrini *et al.*, 2011) and asymbolia for pain (Berthier *et al.*, 1988). In the latter disorder, whose first-ever description also mentioned self-mutilative behaviour (Schilder and Stengel, 1928), damage to the inferior parietal lobule was invariably accompanied by insular lesions (Berthier *et al.*, 1987, 1988), arguably suggesting a disconnection between (para)limbic and cortical areas (Geschwind, 1965; Mesulam and Mufson, 1985). In experimental paradigms used to provoke limb disownership, the inferior parietal lobule is reportedly involved (Kammers *et al.*, 2009), especially when the procedures require participants' response to noxious or threatening stimulation (Lloyd *et al.*, 2006). Furthermore, healthy subjects' ability to discriminate between self and non-self can be impaired by transcranial magnetic stimulation over the right inferior parietal lobule specifically (Uddin *et al.*, 2006). We have located a cluster with increased cortical

thickness and volume in the more lateral inferior parietal lobule of our participants with xenomelia. This may point to local brain tissue reorganization as a consequence of some compensatory mechanism (Maguire *et al.*, 2000; Draganski *et al.*, 2006).

Parts of xenomelia participants' right anterior insular cortex and frontal operculum proved to be of smaller area than the corresponding regions of the control participants' brains. Even if a multitude of heterogeneous functions have been localized to the insula (Craig, 2009), homeostasis and interoceptive awareness are among the most prominent functions associated with this part of the brain (e.g. Craig, 2002; Critchley *et al.*, 2004). This role of the insula makes it an integral part of the body matrix and key to bodily self-awareness (Tsakiris *et al.*, 2007). A previous study described a positive correlation between awareness scores derived from a 'Body Perception Questionnaire' and the volume of the right anterior insular cortex/operculum in 25 healthy participants (Critchley *et al.*, 2004). The authors concluded that the insular/opercular complex of the right hemisphere forms the neuroanatomical substrate for an interoception-based conscious representation of the bodily self. In direct connection with xenomelia, Brang *et al.* (2008) postulated a key role of the insula for the genesis of xenomelia. They observed that touch distal to the demarcation line, which constitutes the border between accepted and non-accepted body territory, elicited an exaggerated galvanic skin response in persons with the disorder. This pathologically enhanced autonomous response, Brang *et al.* (2008) argued, would reflect the mismatch between spared bottom-up somatosensory information from SII to the insula and a deficient higher-order representation of the body part in the superior parietal lobule, reciprocally interconnected with the anterior insular cortex.

Finally, participants with xenomelia showed a smaller surface area in both right SI and SII. On first consideration, it may seem surprising that structural correlates of xenomelia would comprise such low-level somatosensory areas as SI and SII. Although paresthesias and similar misperceptions in the somatosensory domain can occur in subjects with xenomelia (Blanke *et al.*, 2009), no such symptoms were reported by any of our participants. Also, no primary sensory deficit was evident in our thorough neurological status examination. It is therefore unlikely that aberrant signalling by a dysfunctional SI to higher-order areas of tactile integration forms the primary origin of the desire for amputation. Rather, SI surface area may be reduced in response to diminished or distorted back projections from the superior parietal lobule via SII.

Cortical surface area and cortical thickness can be associated with distinct cellular features of the cortical organization. The radial unit hypothesis postulates that cells within a cortical column share a common origin and migrate to their location within the cortex during neural development (Mountcastle, 1997; Rakic, 1988, 2007). This hypothesis further assumes that the number of columns (or, alternatively, their size and spacing) drives the size of the cortical surface area, whereas the number of cells (or alternatively their size and spacing) within a column influences cortical thickness (Rakic, 1988). Therefore, we assume that a change in cortical surface area as observed in subjects with xenomelia in the present study is a marker for the number, the size and/or the spacing of cortical columns, whereas a change

in cortical thickness is a marker for number, size and/or spacing of cortical cells within columns.

Limitations of the present study

Several limitations of the present study warrant discussion. First, sample sizes were rather small, and accordingly the statistical power to detect a particular effect was modest. However, given the rarity of xenomelia, a sample of 13 affected persons is still considerable, especially in view of the relative uniformity of the amputation desire in this sample (lasting for many years and targeting the legs in all cases). Second, although the effects reported did not survive a stringent correction for multiple comparisons, it is unlikely that they represent false positives because the locations of structural alterations were predicted on the basis of published findings. We emphasize, however, that any correction procedure may protect from type I errors, but only at the expense of enhancing the risk for type II errors (Lieberman and Cunningham, 2009). We also applied a conservative cluster extent threshold of $k > 25 \text{ mm}^2$. This protected against spurious findings as false positives do not cluster in space. Limiting our analyses to parietal and insular cortex prevented us from considering potential structural differences in other regions of the cortex and especially also in subcortical structures. This shortcoming should be addressed in future investigations with larger samples.

Another potential point of critique concerns our choice of terminology. On the one hand, the term 'xenomelia' (McGeoch *et al.*, 2011) may be preferred over the older, more interpretative expression 'body integrity identity disorder'. However, body integrity identity disorder comprises a broader scope of symptoms, including the desire for paraplegia (Giummarra *et al.*, 2012) and for other functional impairments, such as deafness (Veale, 2006). Xenomelia may well constitute just one expression of a more general disturbance of a functionally intact bodily self. In this respect, the grey matter correlates we found in the present sample may not be generalized to body integrity identity disorder in the broader sense. We finally point out that participants with xenomelia tended to be more impulsive than control subjects, and they had slightly, although non-significantly, elevated scores on inventories assessing dissociative and borderline symptoms. This is a novel finding, but should be interpreted with caution; any tendency may entirely be due to those items in the respective inventories that directly address the very state of xenomelia (Supplementary Table 1).

Finally, a word of caution seems in place concerning a too unilateral interpretation of the data reported here. They should by no means be taken as evidence for the view that behavioural abnormalities necessarily originate in structural abnormalities. Some clinical observations in selected individuals with xenomelia cannot readily be accounted for by reference to neurological mechanisms alone (Oddo *et al.*, 2009; Kasten and Stirn, 2010; Sedda, 2011). It could well be possible that the specific structural features reported here are the consequence and not the cause of xenomelia. Because we know that the human brain is highly plastic (Jäncke, 2009), the grey matter peculiarities found in the present study could be due to the lifelong adaptation of the brain to the particular needs and desires of the persons with xenomelia. If

a reduction in cortical thickness can be observed in response to a mere 2 weeks of limb immobilization (Langer *et al.*, 2012), it should not be surprising that years of continuous rejection of certain body parts are reflected in relatively circumscribed neuroarchitectural changes. Whether such changes may be pronounced in those with a chronic underuse of the undesired limb(s) (not present in our sample, but see Riordan and Appleby, 1994) or with a particularly longstanding history of pretending behaviour, needs to be explored in future studies.

Conclusion

In 13 individuals with xenomelia, we described distinct alterations in the cortical architecture of the parietal lobe, predominantly of the right hemisphere, and the right anterior insula. These findings suggest that the desire for healthy limb amputation is the consequence of a breakdown in a network subserving the establishment and maintenance of body ownership. Lateralization of this network to the right hemisphere explains the strong preponderance of left-sided limbs as the target site of the amputation desire, and the established co-occurrence of this desire with an erotic attraction by amputees may point to intracortical or parieto-limbic hyperconnectivity. However, our findings do not fully illuminate the ontogenetic path that leads an individual to contemplate the amputation of an intact limb. Without further data we cannot know whether the structural anomalies described here are the cause or the consequence of xenomelia. Some observations speak in favour of an innate representation of a four-limbed human body form, which seems to be defective in xenomelia. Other observations instead support the view that decades of attentional fixation to a particular limb may have altered its cortical representation. What appears undisputed is that the desire for healthy limb amputation, as difficult as it may be to empathize with, is clearly imprinted in the human brain.

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Supplementary material

Supplementary material is available at *Brain* online.

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