



Shape alterations of basal ganglia and thalamus in xenomelia



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ABSTRACT

Xenomelia is a rare condition characterized by the persistent desire for the amputation of physically healthy limbs. Associations with morphological alterations such as reduced cortical thickness and surface area. Nothing is known, however, about the potential involvement of subcortical structures. The thalamus and basal ganglia process, relay, and integrate sensorimotor information and are involved in the preparation and execution of movements. Moreover, both of these structures house somatotopic representations of all body parts.

We therefore investigated subcortical correlates of xenomelia by assessing basal ganglia and thalamus by means of vertex-wise shape analyses. For that purpose, we compared the shape of the thalamus, putamen, caudate nucleus, and the pallidum in 13 men suffering from xenomelia, all desiring a leg amputation, compared to 13 healthy control men. We hypothesised that the target leg is misrepresented in subcortical structures of individuals with xenomelia, especially in locations with a somatotopic representation.

Shape analyses showed thinning of bilateral dorsomedial putamina, left ventromedial caudate nucleus and left medial pallidum associated with xenomelia. This was accompanied by thickening of bilateral lateral pallida and the left frontolateral thalamus. These shape differences were mainly located in sensorimotor areas of somatotopic leg representations.

The present study provides strong evidence for shape differences in striatal, pallidal, and thalamic subregions housing subcortical body part representations. It adds to previously described neural correlates of a condition one can barely empathize with and invites future connectivity analyses in cortico-subcortical networks.

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1. Introduction

A good decade ago, the American psychiatrist Michael First described a peculiar disorder he dubbed “body integrity identity disorder” (BIID) (First, 2005). Persons with BIID are dissatisfied with their body and its functionality. Since childhood or early adolescence they feel that they are “in the wrong body” and are increasingly longing for a live as a disabled person, striving for limb amputation, paraplegia or functional impairments such as deafness or blindness (First and Fisher, 2012). Xenomelia (McGeoch et al., 2011) is one variant of BIID. As its Greek-derived label suggests (xeno stands for “foreign” and melos for “limb”), it consists in the feeling that one or more limbs do not belong to the bodily self. Individuals with xenomelia typically report that they would feel “more complete” if their unwanted limb had been

removed (Blanke et al., 2009). While it is hard to empathize with such feelings and desires, extensive psychiatric examination of participants suffering from xenomelia showed a normal mental status and, in particular, the absence of any psychotic disorder (First, 2005; Hilti et al., 2013; van Dijk et al., 2013). In fact, persons affected with the condition feel themselves embarrassed about the bizarreness of their desire for amputation and usually keep it secret. Internet communities have helped them with their “coming out”, which has let some researchers claim that BIID is a clinical entity largely manufactured by the Internet (Charland, 2004). However, scattered reports about early cases of BIID e.g. (Money et al., 1977; Wakefield et al., 1977) clearly show that, even if social media may significantly influence incidence and manifestation of the disorder (Brugger et al., 2013; Davis, 2012), the biological basis of BIID cannot be denied.

Aetiology and pathophysiology of BIID in general and xenomelia in particular are currently unknown. Most medical practitioners are unfamiliar with the affliction and, when confronted with a patient desiring the amputation of a healthy and fully functional limb, will find themselves to be at their wits' end. Manuals of mental disorders will not provide assistance in a diagnosis, as the proposal to include the disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was

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turned down in a late decisional phase (Zucker, 2013). This nosological and diagnostic palsy helped mushroom attempts to “neurologize” the disorder on insufficient empirical grounds. For instance, the superficial phenomenological similarity between somatoparaphrenia (Vallar and Ronchi, 2006) and xenomelia as acquired vs. innate forms of an absent ownership over a body part has led to the assumption of a conceptual relatedness (Brang et al., 2008). The denial of ownership over paralyzed limbs is seen after right parieto-insular lesions and can be transiently alleviated by neuro-otological procedures (Rode et al., 1992). However, recent empirical work has shown that these procedures do not influence the strength of the desire for amputation (Lenggenhager et al., 2014), questioning the value of hastily comparisons between somatoparaphrenia and xenomelia, specifically with respect to the claimed suitability of common intervention methods (Ramachandran and McGeoch, 2007). Nevertheless, a neurological origin of xenomelia was suggested by recent empirical research. Among the first to seek empirical evidence for its neurological roots were Brang and colleagues (Brang et al., 2008). In that study, pinpricks to two individuals suffering from the condition have been applied and the authors reported an abnormally strong galvanic skin response evoked by the stimulation of the undesired compared to the accepted parts of their bodies. This has been interpreted as resulting from a pathologically exaggerated sympathetic outflow from areas of the limbic system such as the insula to the parietal cortex. This sympathetic hyper-responsibility might have interfered with the formation of a proper representation of the unwanted limb during early brain development. Therefore, the desire for amputation might be the direct consequence of a misrepresentation of a particular body part, despite the fact that their participants' limbs showed intact primary sensory and motor functions (Brang et al., 2008).

In a subsequent study with four persons suffering from xenomelia, magnetoencephalographic signals to tactile stimulation below and above the line of desired amputation have been recorded. In contrast to touch on accepted body parts, touch on the undesired limb failed to elicit a cortical response in one particular brain area, i.e. the right superior parietal lobule (SPL; (McGeoch et al., 2011)). It has been suggested that this part of the parietal lobe is the core region for establishing and maintaining a coherent sense of having a body, i.e. the body image (Berlucchi and Aglioti, 2010; Giummarra et al., 2008; Moseley et al., 2012).

Intriguingly, a structural imaging study in participants suffering from xenomelia using surface-based morphometric procedures (Hilti et al., 2013) identified neuroarchitectural anomalies in exactly those cortical areas, i.e. in the right anterior insula (Brang et al., 2008) and the right SPL (McGeoch et al., 2011). Decreased cortical surface area in the right primary somatosensory (SI) cortex representation of the left leg and in the right secondary somatosensory (SII) cortex has been reported in addition (Hilti et al., 2013).

While our previous work had been confined to cortical structures (Hilti et al., 2013), we here set out to investigate subcortical correlates of xenomelia by assessing the basal ganglia and thalamus by voxel-based volumetric analysis as well as by means of vertex-wise shape analyses (Patenaude, 2007; Patenaude et al., 2011). For that purpose, the shapes (and volumes too) of the putamen, pallidum, caudate nucleus, and the thalamus derived from 13 participants with xenomelia (the same as in (Hilti et al., 2013)), all of whom desiring an amputation of one or two legs, have been compared with those of 13 healthy control men.

We hypothesised that the faulty cortical representation of the unwanted limb would also manifest itself on a subcortical level, notably by local volume and/or shape differences, i.e. either by a negative local tissue displacement (local “thinning”) and/or a positive local tissue displacement (local “thickening”) of thalamic and basal ganglia structures known to house somatotopic representations of feet and legs (Bingel et al., 2004; Gerardin et al., 2003; Lehericy et al., 1998).

2. Material and methods

2.1. Subjects and study design

Thirteen men suffering from xenomelia were recruited via an Internet site. Their medical history was free of any neurological and psychiatric disease, and thorough neurological and psychiatric examinations proved normal (Hilti et al., 2013). We also recruited control subjects who did not differ from the xenomelia group with respect to sex, handedness, footedness, age, and education. The participants with xenomelia all desired an above-knee amputation; eight of the left leg, two of the right leg, and three participants desired the amputation of both legs. All subjects suffering from xenomelia completed the Zurich Xenomelia Scale (Aoyama et al., 2011), a 12-item questionnaire that assessed the degree of xenomelia and that of associated symptoms such as the erotic attraction by amputees and the urge to pretend to be an amputee (Brugger et al., 2013).

The study protocol complied with the Declaration of Helsinki and was approved by the local ethics review board of the University Hospital Zurich. All study subjects provided written informed consent prior to participation.

2.2. Magnetic resonance imaging data acquisition

Scans were acquired on a 3.0 Tesla Philips Achieva whole-body scanner (Philips Medical Systems, Best, The Netherlands) equipped with a transmit-receive body coil and a commercial eight-element sensitivity encoding (SENSE) head coil array. For each participant, 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 coregistered and averaged to increase both the signal-to-noise as well as the contrast-to-noise ratio.

2.3. FMRIB's integrated registration and segmentation tool (FIRST)

FMRIB's Integrated Registration and Segmentation Tool (abbreviated as FIRST, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST>) (Patenaude, 2007; Patenaude et al., 2011) is a computerized and in the FMRIB's software library (FSL) implemented (Smith et al., 2004) subcortical segmentation tool based on T1-weighted MRI scans using shape and appearance models. On the one hand, FIRST performs volumetric analyses indicating changes in the overall volume of each subcortical structure between different groups or across time. On the other hand, FIRST conducts vertex-wise analyses showing the location of differences in the shape of subcortical structures between different groups (Brian et al., 2007, 2008; Fernandez-Espejo et al., 2010; Morey et al., 2010; Patenaude, 2007; Patenaude et al., 2011; Seror et al., 2010).

2.4. Structural and landmark information for shape analysis

The structural and landmark information of the shape models in FIRST were constructed from manually segmented and labelled T1-weighted images of the brain from 336 subjects, comprising the whole spectrum from children to adults (age range: 4–87 years) as well as pathological populations including schizophrenia and Alzheimer's disease participants. All these brain images have been provided by the Center for Morphometric Analysis, Massachusetts General Hospital in Boston, USA (<http://www.cma.mgh.harvard.edu>). The manually generated volumetric labels were parameterized by a 3D deformation of a surface mesh model based on multivariate Gaussian assumptions and then modelled as a point distribution model in which the geometry and variation of the shape of the structures were submitted as prior

anatomical information (Erickson et al., 2009; Morey et al., 2010; Patenaude, 2007; Patenaude et al., 2011).

2.5. Processing steps for extracting shape information

For the vertex-wise shape and volumetric analysis only the right and left pallidum, putamen, caudate nucleus and thalamus were selected. The subcortical segmentations were performed in the following steps. First, the `run_first_all` command was conducted restricted to the aforementioned structures by specifying the boundary correction method. This single command registered the images to the MNI152_1 mm template (part of FSL), segmented all the subcortical structures, fitted structure models (meshes) to the image and applied the specified boundary correction (in our case FAST). The FMRIB's automated segmentation tool (FAST) was used as the boundary correction option (Zhang et al., 2001) as recommended by Patenaude and colleagues (Patenaude, 2007; Patenaude et al., 2011). FAST was used to determine whether the voxels located at the boundary of the shape models are part of the structure or not. This is important especially for structures that are in close neighbourhood to each other such as the putamen and pallidum on one hand and the thalamus and caudate nucleus on the other hand. The final stage of the script ensured that there were no overlaps between different structures in the 3D image (such could occur even when there is no overlap of the meshes). After that, it has been verified whether the registration and the subsequent segmentation were successful by assuring that there were no errors in the log files. Nevertheless, using the relevant `slicesdir` tool (part of FSL), we carefully checked the resulting registration of the subjects' brains onto the templates. Paying particular attention to the subcortical structures, it was noticed that the outputs of the summary results for each subject's registration looked well. Afterwards, segmentations were also evaluated with the `first_roi_slicesdir` command. For each subject the `run_first_all` script produced *.vtk files (mesh representations of the final segmentation), *.bvars files (which contain model parameters and the model used, which is important to perform the vertex-wise shape analysis) and *.nifti files (volumetric outputs for the volumetric analysis). After having concatenated the *.bvars files across subjects, the vertex-wise shape analysis was performed with the `first_utils` command that aims at assessing group differences in shape/displacement on a per-vertex basis. For more information about the fitting procedure for the mesh models including the mathematical formulas and algorithms the reader is referred to the relevant literature (Patenaude, 2007; Patenaude et al., 2011) as well as to the website of the FIRST tool used for our shape analyses (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST>).

2.6. Statistical analyses

Statistics were done with the `randomise` tool (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise>) by defining univariate t-contrasts, corrected for multiple comparisons by applying 5000 permutations of the group label across space. The contrasts investigated were xenomelia > controls (positive tissue displacements, implying that xenomelia participants have a locally larger structure than controls, i.e. local thickening of a particular structure in xenomelia) and controls > xenomelia (negative tissue displacements, implying that xenomelia participants have a locally smaller structure than controls, i.e. local thinning of a particular structure in xenomelia). It is important to note that FIRST uses the vertices only internally to run the vertex-wise shape analysis. The vertices are then projected back into a volume in order to run the non-parametric statistics in FSL's `randomise` tool, which cannot deal with meshes. The result is a volumetric image for the statistics; this is what should be interpreted and has been interpreted here.

The significant contrasts were visualized by loading them in the 3D viewer of FSL, but these results were only displayed on the structure's surface. Therefore, 3D mesh outputs displaying the results of the vertex analysis were visualized as well. The mesh outputs were obtained by adding the `-surfaceout` option to the `first_utils` command, but are based on a multivariate F-statistic because those outputs use an old vertex-wise analysis method that is no longer recommended for statistical analyses (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST>), but can still be used to visualize shape differences (magnitude and direction) and has therefore been applied in the present study. The surface coloring is the multivariate F-statistic (based on Pillai's trace). The length of the vectors and the statistics are not linearly related - the former is dependent only on the mean difference between groups while the latter is a statistic that takes the variances into account (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST>).

Furthermore, a volumetric analysis was performed with `fsstats`, specifying this command with the respective label number of the structures of interest, which are visible on <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide>. Thereafter, the values obtained from `fsstats` (overall volume of each subcortical structure) were exported to IBM SPSS Statistics (version 22.0, <http://www-01.ibm.com/software/analytics/spss/>) and independent-samples two-tailed t-tests have been applied. Demographic, xenomelia-related, psychiatric as well as global brain measures have been compared using t-tests for independent samples. If not otherwise stated, two-tailed p-values are reported.

3. Results

3.1. Demographic, xenomelia-related, psychiatric, and global brain measures

Demographic, psychiatric, global brain and xenomelia-related measures of the 13 participants suffering from xenomelia and the 13 healthy control men can be found in Table 1 and also elsewhere (Hilti et al., 2013).

Spot-like descriptive examples of xenomelia patients' answers to psychiatric and xenomelia-related questionnaires can be found elsewhere (Blom et al., 2012). Some psychiatric questionnaires (dissociative symptoms, Barrat impulsivity scale, and borderline symptom list), however, revealed statistical trends ($0.05 < p < 0.10$, uncorrected for multiple comparisons) towards higher values in xenomelia participants relative to control men. However, there were items that specifically asked for the rater's dissatisfaction with the own body or parts of it, and these items inflated the results of those questionnaires. These statistical tendencies towards increased values in participants disappeared after such xenomelia-relevant items have been removed from the questionnaires.

In the following paragraphs, we first report the results of the shape analyses followed by the results of the volumetric analyses. The subcortical brain structures showing significant shape differences between participants suffering from xenomelia and control men are summarized in Table 2.

Below we report the shape differences in more detail and also visualize the findings in two different ways.

3.2. Shape analysis of the striatum

A cluster in the dorsomedial part of the left putamen showed local thinning in participants suffering from xenomelia compared with control men (Figs. 1 and 2).

The significantly ($p = 0.005$, corrected for multiple comparisons) thinner dorsomedial part of the left putamen (MNI peak coordinates: $x = -21$, $y = -2$, $z = 7$) in xenomelia participants is located in that part of the putamen, which represents foot movement activity as has been reported by Gerardin and colleagues (Gerardin et al., 2003) (MNI

Table 1
Demographic, xenomelia-related, global brain, and psychiatric measures of the participants under investigation.

Demographic and xenomelia-related measures	Participants with xenomelia (n = 13)		Control participants (n = 13)		t-value	p-value
	Frequency		Frequency			
Handedness (right/left/ambi)	12/1/0		12/1/0			
Footedness (right/left/ambi)	12/1/0		12/1/0			
Sexual orientation (hetero/homo/bi)	6/5/2		13/0/0			
Target leg (left/right/both)	8/2/3		n.a.			
Amputation desire since (years/I can remember)	7.86 y./2 p.		n.a.			
Height of desired amputation (AKA/BKA)	13/0		n.a.			
Triggering events (encounters with amputee(s)/no event)	9/4		n.a.			
	Mean	SD	Mean	SD		
Age, education and global brain measures						
Age (years)	49.3	14.5	50.2	12.5	−0.16	0.87
Education (years)	15.4	3.0	14.8	2.8	0.85	0.40
Total intracranial volume (cm ³)	1509.3	218.1	1510.2	172.1	−0.01	0.99
Total gray matter volume (cm ³)	642.2	43.5	627.5	50.9	0.79	0.44
Total subcortical gray matter volume (cm ³)	185.5	13.8	178.8	23.1	0.90	0.38
Total left white matter volume (cm ³)	263.8	21.1	258.8	23.5	0.58	0.57
Total right white matter volume (cm ³)	262.0	24.5	259.1	24.0	0.30	0.76
Total left cortical volume (cm ³)	232.8	16.9	227.7	20.3	0.70	0.49
Total right cortical volume (cm ³)	232.0	18.3	228.8	19.8	0.44	0.66
Total left cortical surface area (cm ²)	856.9	52.9	849.3	60.5	0.34	0.74
Total right cortical surface area (cm ²)	849.4	59.5	848.0	59.9	0.06	0.95
Mean left cortical thickness (mm)	2.462	0.110	2.452	0.078	0.27	0.79
Mean right cortical thickness (mm)	2.479	0.115	2.473	0.079	0.30	0.89
Xenomelia-related and psychiatric measures						
ZXS - amputation desire	5.15	0.59	n.a.	n.a.	n.a.	n.a.
ZXS - erotic attraction	4.73	1.12	n.a.	n.a.	n.a.	n.a.
ZXS - pretending behaviour	3.88	1.14	n.a.	n.a.	n.a.	n.a.
ZXS - total score	4.59	0.61	n.a.	n.a.	n.a.	n.a.
Body dysmorphic disorder	23.9	7.9	24.1	6.0	−0.77	0.94
Borderline symptom list	63.8	27.9	44.6	22.5	1.93	0.07
Obsessive-compulsive inventory, revised	11.9	5.9	11.0	10.2	0.28	0.78
Schizotypal personality questionnaire (SPQ-G factor 1)	8.7	6.2	10.8	9.4	−0.69	0.50
Schizotypal personality questionnaire (SPQ-G factor 2)	13.5	9.2	16.0	11.2	−0.17	0.86
Schizotypal personality questionnaire (SPQ-G total score)	4.8	5.1	5.2	3.8	0.61	0.55
Barratt impulsiveness scale	38.8	4.5	33.5	8.8	1.90	0.07
Depression anxiety stress scale	14.9	11.2	15.8	13.5	−0.19	0.85
Dissociative symptoms	322.3	241.2	174.5	155.8	1.86	0.08
Personal attributes questionnaire (Mascul./Femin.)	43.3	2.7	42.1	3.4	1.03	0.31
Gender identity	59.2	8.2	60.2	8.9	−0.28	0.79
Bem sex role inventory	219.2	17.1	216.8	21.5	0.32	0.75

Notes: AKA, above knee amputation; BKA, below knee amputation; ZXS, Zurich Xenomelia Scale.

peak coordinates: $x = -30$, $y = 0$, $z = 10$). There was also a trend ($p = 0.063$, corrected) towards a thinner right dorsomedial putamen. Additionally, a trend ($p = 0.060$, corrected) towards local thinning of the left ventromedial caudate nucleus was found in participants with xenomelia and is depicted in Fig. 2.

3.3. Shape analysis of the pallidum

A cluster revealing a significantly ($p = 0.039$, corrected) thicker left lateral pallidum in xenomelia participants compared to control subjects has been found (Figs. 3 and 4).

Moreover, there was a cluster showing a trend ($p = 0.057$, corrected) towards a dilatation of the shape of the right pallidum in participants with xenomelia compared to control men (Fig. 4). As depicted in Fig. 4, the obtained findings are partly situated in the motor territories of the pallidum, which reportedly contain a somatotopic foot representation (Nambu et al., 2011).

Additionally, in the left pallidum, individuals with xenomelia demonstrated a trend ($p = 0.051$, corrected) towards a smaller medial pallidum (MNI peak coordinates: $x = -18$, $y = -7$, $z = 3$). This cluster seems to be located in the internal globus pallidus.

3.4. Shape analysis of the thalamus

Two clusters situated in the left frontolateral thalamus showed significant ($p = 0.029$ and $p = 0.043$, both corrected) thickening for participants with xenomelia compared to control men (Figs. 5 and 6).

This significant contrast is depicted in Fig. 6 in a 3D view and illustrates that this cluster is located in the area of the ventral anterior and ventral lateral thalamic nuclei, which is connected to motor cortical areas.

3.5. Volumetric analyses

The volumetric analyses revealed neither significant group differences nor trends in the thalamus, caudate nucleus, putamen and pallidum and are therefore not presented nor further discussed here.

4. Discussion

A vertex-wise shape analysis based on shape and appearance models within a Bayesian framework implemented in the FIRST software tool demonstrated several structural brain alterations in form of

Table 2
Basal ganglia and thalamus clusters with locally altered shape in participants with xenomelia compared to control men.

Altered shape Structure	# Voxels ($1 \times 1 \times 1 \text{ mm}^3$)	Error Probability	MNI coordinates		
			x	y	z
Thickening in xenomelia					
Left pallidum	51	0.039	-24	-4	0
Right pallidum	139	0.057*	27	-11	2
Left thalamus	87	0.029	-12	-3	9
Left thalamus	27	0.043	-17	-8	10
Thinning in xenomelia					
Left pallidum	107	0.051*	-18	-7	3
Left caudate nucleus	36	0.060*	-12	-2	13
Left putamen	323	0.005	-21	-2	7
Right putamen	154	0.063*	23	-4	6
Right putamen	2	0.098*	27	-8	-8

Note. Results obtained from vertex-wise shape analysis with FIRST. Error probability was set at $p < 0.05$ corrected for multiple comparisons using 5000 permutations of the group label across space. MNI, Montreal neurological institute.

* Indicates effects that were statistically significant only on a trend level ($0.05 < p < 0.10$, corrected).

structure tissue displacements between xenomelia participants and healthy control men. Compared with control participants, participants suffering from xenomelia featured the following local shape alterations: they showed a significantly thinner left dorsomedial putamen and a trend towards a thinner right dorsomedial putamen. They also exhibited a trend towards a thinner left ventromedial caudate nucleus. Regarding the pallidum, they showed a trend towards a thinner left medial pallidum and a significantly thicker left lateral pallidum. Additionally, there was a trend towards a thicker right lateral pallidum. The participants with xenomelia also showed a significantly thicker left frontolateral thalamus compared with the thalamus of healthy control men.

4.1. Interpretation

Xenomelia participants showed a significantly thinner left dorsomedial putamen and a trend towards a thinner right dorsomedial

putamen, consistent with atrophy in these regions. These local atrophies in xenomelia participants, who all desired a leg amputation, overlap with the region activated during foot movement (see Fig. 2) as measured with functional magnetic resonance imaging (Gerardin et al., 2003). Hence, it is reasonable to link our structural finding to a compromised leg representation in xenomelia. The major loci of shape alteration (MNI peak coordinates: $x = -21$, $y = -2$, $z = 7$ and $x = 23$, $y = -4$, $z = 6$) are located more medial to the activation maximum as has been reported by Gerardin and colleagues (MNI Peak-coordinates: $x = -30$, $y = 0$, $z = 10$) (Gerardin et al., 2003). The legs are usually represented in a dorsolateral zone, which receive input from M1. However, the legs are also represented in the dorsomedial part of the putamen, conforming to inputs from SMA. Interestingly, the right SMA is known to show increased activation to tactile stimulation of xenomelia participants' legs, irrespective of which leg is accepted or rejected (van Dijk et al., 2013). It might be possible that the underrepresentation of xenomelia participants' legs in the putamen is compensated in the SMA and, therefore, the SMA shows a neural over-activation.

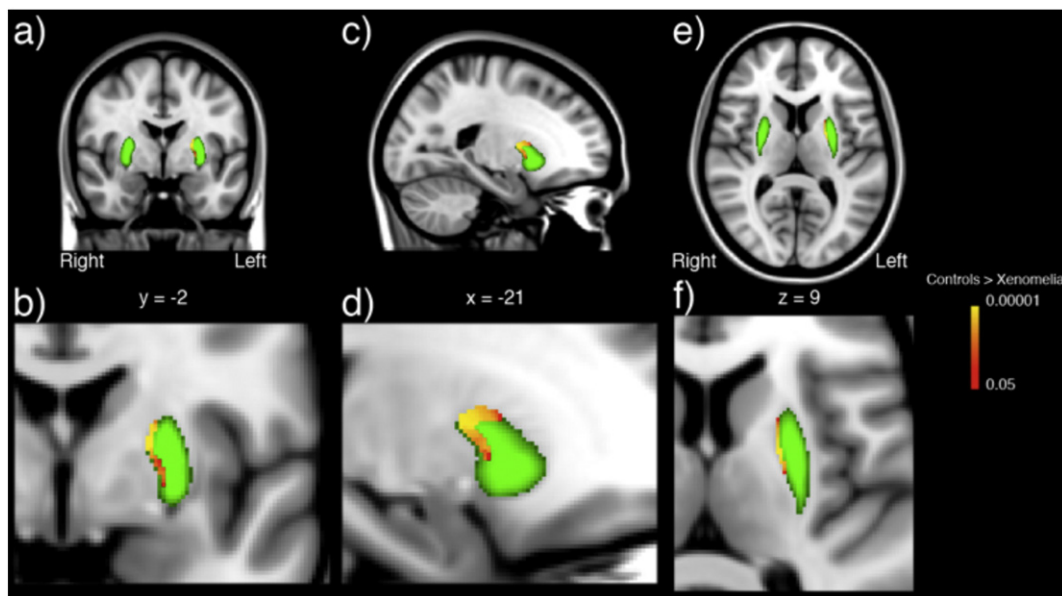


Fig. 1. Local thinning of the left putamen in xenomelia. A cluster showing significant dorsomedial thinning (red-yellow) of putamen (green) in participants with xenomelia compared with healthy control men. Error probability was set at $p < 0.05$ corrected for multiple comparisons using 5000 permutations of the group label across space. The shape differences and putamen masks are overlaid on the MNI152 T1-weighted template. a) Coronal plane unzoomed b) coronal plane zoomed c) sagittal plane unzoomed d) sagittal plane zoomed, e) axial plane unzoomed, f) axial plane zoomed. x, y, z, coordinates of the Montreal neurological institute (MNI) space. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

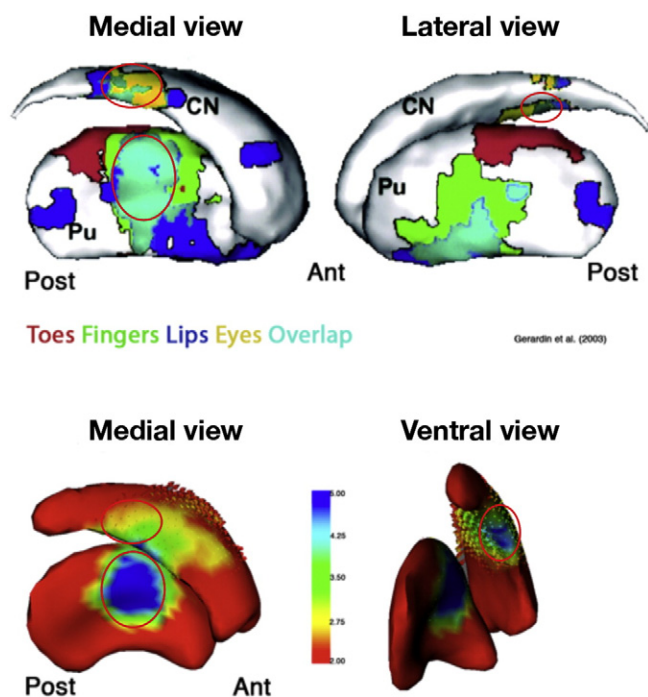


Fig. 2. Three-dimensional view of the left putamen and the left caudate nucleus in xenomelia. Top row: Somatotopic representation of toe, finger, lip and eye movement onto the surface of the left putamen (Pu) in medial and lateral view. Bottom row: 3D surface model of the left putamen and caudate nucleus (NC), showing differences between xenomelia patients versus controls at each vertex on the surface. Note: the surface coloring is the multivariate F-statistic (see text). A rise from lower to higher statistical significance is indicated as color change from red to blue. In the putamen the vectors point from the mean surface of the control group (outward) to the mean surface of the xenomelia patients (inward); that is why the vectors are not really visible. This indicates local atrophy on the left dorsomedial putamen in participants with xenomelia. Local atrophy is also visible in the left ventromedial caudate nucleus. Red ellipses represent corresponding locations between the panels. Note that the representation of the toes/foot/leg (red in the upper panel) is not visible in its full extent on both the putamen and caudate nucleus because it is covered by the overlap (turquoise in the upper panel). Ant = anterior, Post = posterior. Upper panel adapted from Gerardin and colleagues (Gerardin et al., 2003) with permission from Oxford University Press. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Note that in the investigated sample of xenomelia participants, there is a strong bias for a desired amputation of the left leg (8 out of 13). Therefore, one could expect to find only a contralateral shrinking in the right putamen. However, the same subjects showed reduced cortical surface area in the right S1, in the location of the somatosensory representation for the left foot/leg, but showed alterations in both the left S2 (increased cortical surface area) and right S2 (decreased cortical surface area) (Hilti et al., 2013). Likewise, a contraction was found in both putamina. At least two different lines of evidence might explain bilateral findings in the putamen. First, the contraction in the left putamen might be related to the fact that two of the 13 participants suffering from xenomelia desired a right leg amputation and three desired an amputation of both legs. Unfortunately, the number of participants desiring a right leg amputation or an amputation of both legs is too small to be further statistically investigated. Second, this result can be expected on the basis of previous findings that showed bilateral putamina activation during unilateral foot movement (Sahyoun et al., 2004; Scholz et al., 2000). It is possible that the observed underrepresentation in bilateral putamina occurs due to interconnections between both putamina over the corpus callosum. In monkeys, the M1 inputs to the putamen are stronger than those S1, and only the former are bilateral (Flaherty and Graybiel, 1993). Therefore, in view of the locally contracted right putamen that might result in a compromised somatotopic representation of the affected leg (which is the left one in most cases) in the right S1, information processing and flow might be relayed from the right

putamen's somatotopic leg representation to that of the left putamen resulting in an “underrepresentation” of the affected left leg not only in the contralateral right putamen, but also in the ipsilateral left putamen. A direct relay of information from right somatosensory cortex to the left putamen seems improbable, as primate data suggest that the left putamen receives hardly any somatosensory projections from the right S1 (Flaherty and Graybiel, 1993). Since almost all xenomelia participants of the present sample reported pretending behaviour (Giummarra et al., 2011) to varying extent in their daily life, typically consisting in tying up the left leg and only using the right leg for locomotion, it might finally be conceivable that weaker projections from the right M1, SMA or PMC to the left putamen contribute to an alleged “underrepresentation” of the affected leg.

While bilateral putamina show signs of shrinkage on the dorsomedial side, the lateral sides of both pallida show a thickening in xenomelia participants compared with control men. The left lateral pallidum is significantly thicker and the right lateral pallidum shows a statistical trend towards thickening. These two local shape differences are partly situated in the motor territories of the pallidum showing a somatotopic foot or leg representation (Fig. 4), as demonstrated at least for non-human primates (Nambu et al., 2011). This interesting finding is illustrated in Fig. 7 and explained as follows.

The left lateral pallidum of xenomelia participants exhibits a bulge in the direction of the putamen, whereas the putamen features a notch at exactly the corresponding location. A very similar pattern of tissue displacement (shape difference) has been observed for the thalamus and the caudate nucleus (Fig. 7). The left frontolateral thalamus is significantly thickened in participants with xenomelia compared to control men. This dilatation is located at a region of the thalamus, which is connected to cortical motor areas, namely the ventral anterolateral nucleus. Just above the thickened ventral anterolateral nucleus of the thalamus, the caudate nucleus indicates a local tissue contraction. Combined, the finding of bilaterally thickened lateral pallida as well as a thickened left ventral anterolateral nucleus of the thalamus in xenomelia participants could also be interpreted as a compensatory mechanism. This assumption is strengthened by the findings obtained by Hilti and colleagues. Not only did they find decreased cortical thickness and volume in the right hemisphere, they also described an increased left-hemispheric cortical surface area in S2 and IPL (Hilti et al., 2013). This could point to local brain tissue reorganization as a compensatory mechanism – quite as shown for the hippocampus and parietal cortex in other contexts (Draganski et al., 2006; Maguire et al., 2000).

The basal ganglia are part of the motor loop of the basal ganglia-thalamo-cortico circuit and crucial for the preparation and execution of movements. The focal atrophy of both putamina and the local dilatation of both pallida are located in the so-called motor territories representing legs as described elsewhere (Nambu et al., 2011). These findings might reflect a xenomelia-related motor system alteration. Additional indication for this assumption is provided through a trend towards a local shrinking in regions of the internal globus pallidus in xenomelia participants, whose function is to inhibit motor impulses (Trepel, 2004). Moreover, the thickened frontolateral thalamus concurs with the ventral anterolateral nucleus. This area is connected to cortical motor areas and functionally specialized in processing and integrating motor impulses (Trepel, 2004). A postulated alteration in the motor system of persons with xenomelia was already proposed by van Dijk and colleagues (van Dijk et al., 2013), who showed that tactile stimulation of xenomelia participants' legs leads to abnormally increased activations in brain regions that are involved in the motor system, namely bilateral M1 and right PMv, PMd and SMA.

Unlike the situation in the cortical sensorimotor system where motor and somatosensory information is processed in a segregated way (at least in primary and secondary areas), in the putamen somatosensory and motor information are processed in the same territories. Flaherty and Graybiel showed that homologous parts of the cortical body maps from M1 and S1 converge when they are projected to the

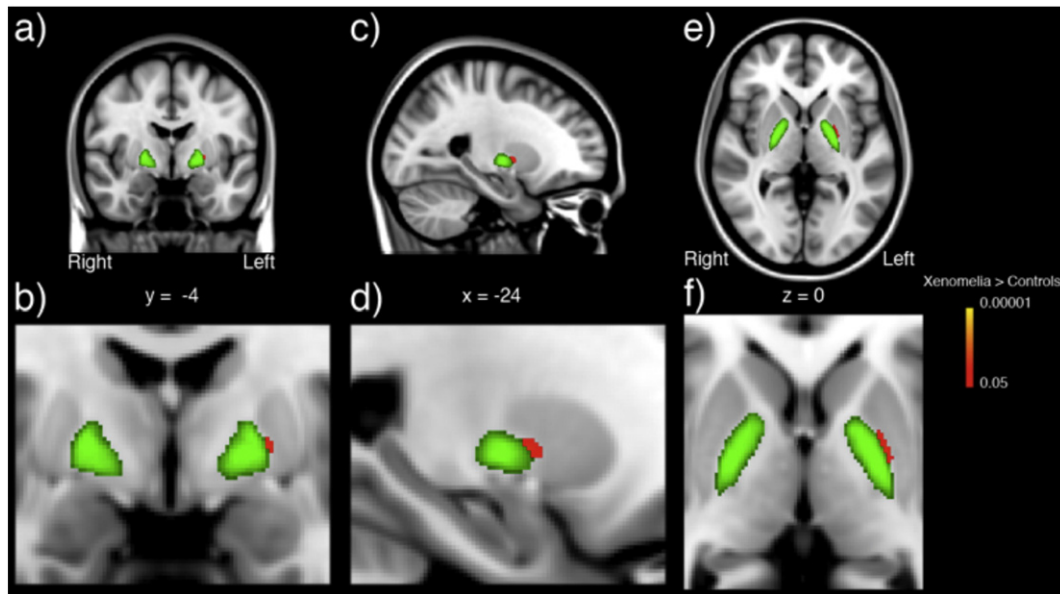


Fig. 3. Local thickening of the left pallidum in xenomelia. A cluster showing a significant thicker lateral (red-yellow) pallidum (green) in participants with xenomelia compared with healthy control men. Error probability was set at $p < 0.05$ corrected for multiple comparisons using 5000 permutations of the group label across space. The shape differences and putamen masks are overlaid on the MNI152 T1-weighted template. a) Coronal plane unzoomed b) coronal plane zoomed c) sagittal plane unzoomed d) sagittal plane zoomed, e) axial plane unzoomed, f) axial plane zoomed. x, y, z, coordinates of the Montreal neurological institute (MNI) space. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

putamen (Flaherty and Graybiel, 1991, 1993, 1995). Thus, it remains indeterminate if a purported xenomelia-related limb misrepresentation at the level of the putamen is linked to sensory or motor information anomalies. However, since the basal ganglia are such important for movement preparation and execution, the present findings suggest that participants with xenomelia have not only an altered sensory, but also an altered motor system on the subcortical level. Although data published by van Dijk and colleagues revealed an involvement of bilateral M1 and right PMv, PMd and SMA in response to tactile stimulation, no significant motor reorganizations on the cortical level have been

observed during a motor execution task (wiggling with the toes) (van Dijk et al., 2013). In this sensorimotor system, xenomelia participants' legs seem to be represented differently. Whether the subcortical structural alterations are the cause or the consequence of the desire for an amputation remains unclear. Nevertheless, it might be possible that *pretending* could reorganize the motor representation of the limbs. In the case of tying up the unaccepted leg, the accepted leg would have to take up the resultant load and therefore the motor representations of the accepted limb could be strengthened and simultaneously that of the unwanted limb reduced. By way of this asymmetry, body map changes consistent with the desired disability could be further reinforced (Giummarra et al., 2011).

It is supposed that information related to unilateral limb movement may be conveyed through the basal ganglia in both hemispheres and converge to the contralateral thalamus (Gerardin et al., 2003). Accordingly, right foot movement activated bilateral putamina, but only the left thalamus, when contrasting the active movement condition from a rest condition (Sahyoun et al., 2004). This functional imaging result matches the findings of the present structural investigation very well. While bilateral putamina exhibit local shape alterations, the thalamus show only left sided shape alterations.

By trend, the ventromedial part of the left caudate nucleus was thinner in xenomelia participants compared to controls. The caudate nucleus delineates functional co-activations with higher-level cognitive areas such as prefrontal brain regions associated with executive functioning. Typically, it shows no clear somatotopic organization of body parts (Grahn et al., 2008; Postuma and Dagher, 2006). Two studies even showed that activity in the right dorsal caudate nucleus was functionally correlated with activity in bilateral IPL (Di Martino et al., 2008; Jung et al., 2014).

The structural shape alterations of the thalamus and basal ganglia can be considered as macrostructural neuronal changes in gray matter (Zatorre et al., 2012). Several cellular level changes, so-called microstructural mechanisms, affect voxel intensities on a T1-weighted image, and therefore, could be the cause of the observed imaging effects. Neuronal changes in gray matter may include dendritic branching, synaptogenesis and axon sprouting (Zatorre et al., 2012). For example, experiments with rats could show that motor skill learning is associated

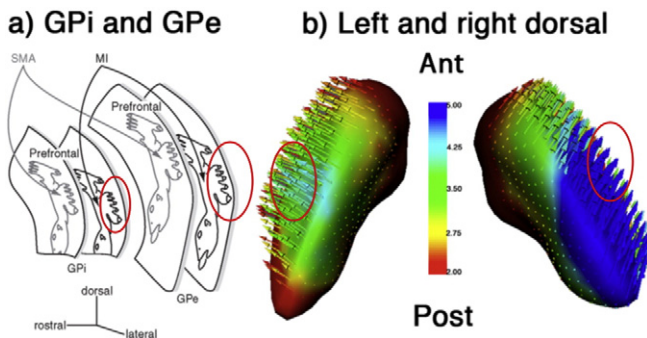


Fig. 4. Three-dimensional view of the pallidum in xenomelia a) Somatotopic representations of the external and internal segments of the pallidum (GPe and GPI, respectively). b) 3D surface output of the left and right pallidum showing differences between controls versus xenomelia participants at each vertex on the surface. Note: the surface coloring is the multivariate F-statistic (see text). A rise from lower to higher statistical significance is indicated as color change from red to blue. The vectors depict the direction of change. In the left pallidum the vectors point from the mean surface of the xenomelia patients group (inward) to the mean surface of the control group (outward), indicating thickening on the left dorsolateral putamen in participants with xenomelia. Analogous presentation for the right pallidum is also shown. When comparing a) and b), the obtained findings are partly located in the motor territory of the pallidum, showing a representation of the foot/legs. Red ellipses represent corresponding locations between the panels. Ant = anterior, Post = posterior. Panel a) adapted from Nambu and colleagues (Nambu et al., 2011) with permission from Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

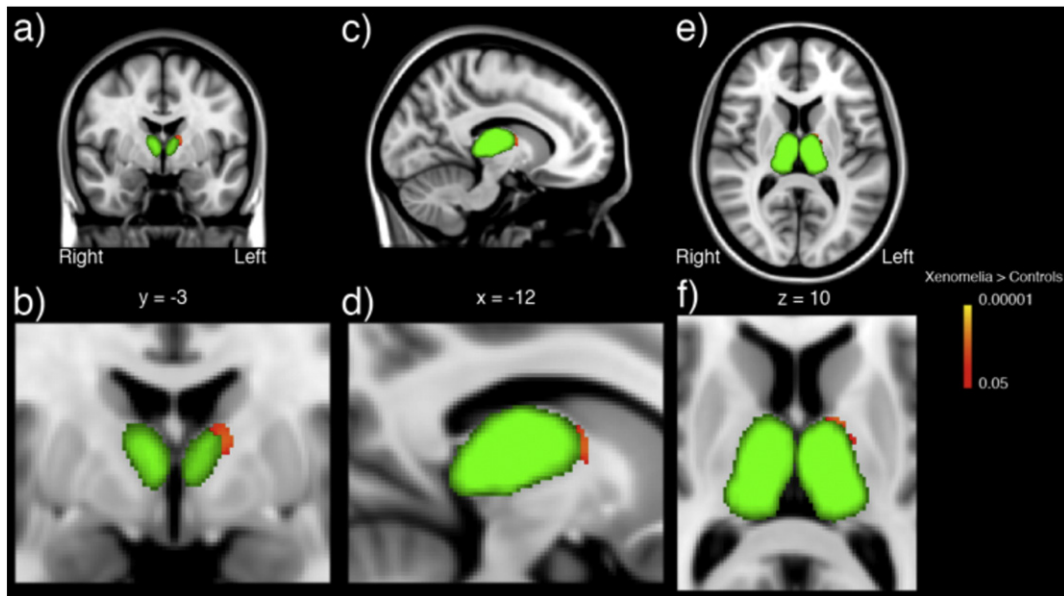


Fig. 5. Local thickening of the left thalamus in xenomelia. Two clusters showing significantly dilated (red-yellow) left frontolateral thalamus (green) in participants with xenomelia compared with healthy control men. Error probability was set at $p < 0.05$ corrected for multiple comparisons using 5000 permutations of the group label across space. The shape differences and putamen masks are overlaid on the MNI152 T1-weighted template. a) Coronal plane unzoomed b) coronal plane zoomed c) sagittal plane unzoomed d) sagittal plane zoomed, e) axial plane unzoomed, f) axial plane zoomed. x, y, z, coordinates of the Montreal neurological institute (MNI) space. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with synaptogenesis (Kleim et al., 2002) and even with changes in dendritic spine morphology (Kolb et al., 2008). Since the thalamus and basal ganglia, key players of the motor system, are altered in xenomelia participants, cellular mechanisms like elimination of synapses could explain a contraction of such structures. In contrast, synaptogenesis could explain the found dilatations. However, neurogenesis is considered a minor factor in MRI-delineated changes (Zatorre et al., 2012). Note, those non-neuronal components such as changes in glial cell number and morphology as well as vasculature (e.g. changes in vascular volume) or angiogenesis also influence MRI signals (Zatorre et al., 2012) and, therefore, could be a further cause of the macrostructural subcortical alteration in xenomelia participants.

Although we found shape differences in the basal ganglia and thalamus between the groups suggesting local tissue displacement in xenomelia, we did not find any statistically significant group differences

in the volumes of these subcortical structures. However, we did not expect any relationship between shape and volume differences because local thinning in one location and local thickening in a neighbouring location does not result in regional volumetric differences as investigated in the present study.

Anatomical alterations in basal ganglia in the form of volume differences have also been reported for other neurological conditions such as Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, and ataxia (Krabbe et al., 2005; Pitcher et al., 2012; Schulz et al., 1999), a fact that might question the specificity of our findings.

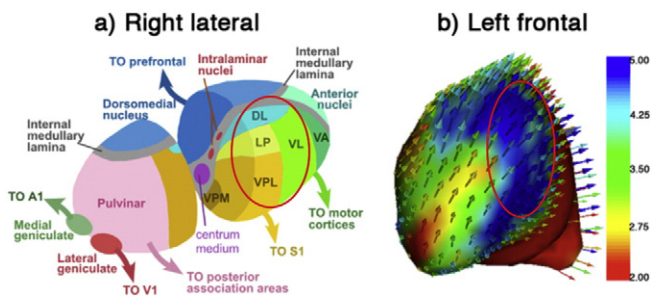


Fig. 6. Three-dimensional view of the left thalamus in xenomelia. a) 3D view of the right lateral thalamus showing different nuclei and their connections to cortical brain regions. b) 3D surface output of the left thalamus showing differences between controls versus xenomelia participants at each vertex on the surface. Note: the surface coloring is the multivariate F-statistic (see text). A rise from lower to higher statistical significance is indicated as color change from red to blue. The vectors depict the direction of change. In the left thalamus the vectors point from the mean surface of the xenomelia participants group (inward) to the to the mean surface of the control group (outward), indicating a thickening of the left frontolateral thalamus in participants with xenomelia. Red ellipses represent corresponding locations between the panels. Left panel adapted with permission from http://www.scholarpedia.org/article/Models_of_thalamocortical_system. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

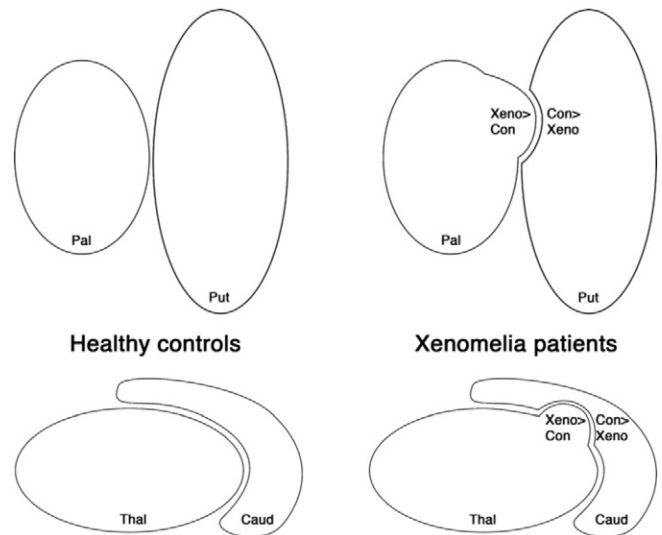


Fig. 7. Schematic illustration of local shape alterations in xenomelia. Left: Putamen and pallidum as well as thalamus and caudate nucleus of healthy controls. Right: Putamen and pallidum as well as thalamus and caudate nucleus of participants with xenomelia. While individuals with xenomelia have a thickening (dilatation) in the lateral pallidum (illustrated by the bulge and indicated by Xeno > Con), they also show a thinning (contraction) in the putamen (illustrated by the notch and indicated by Con > Xeno). The same principle accounts for the thalamus and caudate nucleus. Abbreviations: Put, putamen; Pal, pallidum; Thal, thalamus; Caud, caudate nucleus.

However, for several reasons we think that our results do reflect peculiarities specific to xenomelia. First, in the affected participants we did not find putaminal volume differences similar to those reported in other conditions. Second, the tissue displacements (shape differences) reported seem to be specific in that the shape differences were primarily located in regions devoted to somatosensory information processing while simultaneously sparing regions with other functions. Third, in participants with xenomelia the putamen, caudate nucleus and the thalamus were altered specifically and simultaneously, and this is in contrast to patients suffering from Parkinson's disease where primarily the putamen seems to be affected (Krabbe et al., 2005).

Although a conceptual relatedness between xenomelia and somatoparaphrenia as two types of a loss of body ownership has been emphasized (Brang et al., 2008), the sparse literature on the neurological foundations of these early developmental (xenomelia) versus acquired (somatoparaphrenia) disorders suggests distinguishing neural correlates. In contrast to xenomelia, somatoparaphrenia is often accompanied by hemispatial neglect, hemiplegia, unilateral motor deficits, and anosognosia, suggesting the involvement of different neural circuits. The lesion pattern of somatoparaphrenia involves an extended network comprised by fronto-temporo-parietal regions in addition to the lesions in the white matter, thalamus, basal ganglia, and amygdala (Gandola et al., 2012). It has also been shown that the orbitofrontal cortex is critical in distinguishing somatoparaphrenia from asomatognosia (Feinberg et al., 2010). So far, no evidence for the involvement of frontal brain regions in xenomelia has been reported (van Dijk et al., 2013). Although the insula seems to be affected in both conditions, the right posterior insula is associated with spatial neglect and motor deficits accompanying somatoparaphrenia (Gandola et al., 2012), whereas xenomelia is associated with anomalies in the anterior insula (Hilti et al., 2013; van Dijk et al., 2013). The putamen and pallidum were affected unilaterally only in the right hemisphere in somatoparaphrenia (Gandola et al., 2012), whereas the shapes of these two subcortical structures were bilaterally altered in xenomelia (present study). In our opinion, then, the similarity between xenomelia and somatoparaphrenia primarily rests on clinicians' often over-inclusive attempts at classifying disorders, and lumping together what contains a common element (an impaired sense of body ownership, in the present case). Such emphasis of superficial similarity is certainly helpful in the hypothesis generation and testing phase of an inquiry, but should be abandoned in view of the numerous dissimilarities that may pop up in later scrutinized examinations.

4.2. Limitations

There are several limitations of the present study that are worth mentioning. Firstly, xenomelia is an extremely rare condition. The exact prevalence of persons with xenomelia is not known; worldwide, a few thousand people are assumed to be afflicted (Bayne and Levy, 2005). In view of the rarity of the syndrome, a uniform sample of 13 men, all desiring a leg amputation for many years, is remarkable, and as of today, no other neuroimaging study has ever been reported with a larger sample. However, sample sizes of 13 xenomelia participants and 13 healthy controls are still rather small. Therefore, the statistical power to detect a specific effect was modest. Nevertheless, the reported results, especially from the vertex-wise shape analysis with FIRST, even passed the strict correction for multiple comparisons. This indicates the strength of the obtained findings. We could also not empirically address in how far the fact that not all of our participants wished for an amputation of the *left* leg, might have influenced the laterality of our shape analyses. This is because the sample size of the group desiring a right leg amputation ($n = 2$) as well as that of the group desiring an amputation of both legs ($n = 3$) are obviously too small (also when pooled together $n = 5$) in order to apply any serious statistical test. Secondly, the term xenomelia points to an alienation of one or more of one's limbs. As pointed out in the Introduction, the broader term BIID encompasses a wider range of symptoms, including the desire for paraplegia

(Giummarra et al., 2012) as well as for a range of sensory impairments (Veale, 2006). It is possible that the subcortical structural alterations found in association with xenomelia cannot be generalized to the broader population with BIID. Thirdly, the present study as well as all former neuroimaging studies about xenomelia investigated only men (Brang et al., 2008; Hilti et al., 2013; McGeoch et al., 2011; van Dijk et al., 2013). It remains unclear whether our findings can be extended to the modest number of women, who desire an amputation of a healthy leg (or to the desire for paraplegia, which is relatively over-represented in the female gender (Blom et al., 2012; Giummarra et al., 2012)). Fourthly, with the present structural MRI study, no conclusions can be drawn about the functioning of the thalamus and basal ganglia. It is not known whether the differentially shaped subcortical structures show an abnormal neural functioning. Strictly speaking, it is thus not possible to determine with certainty whether the structural alterations described in the present study indicate a misrepresentation of the affected or the non-affected leg. Lastly, the present investigation is cross-sectional in nature and is not a longitudinal study. Therefore it remains an open question whether the structural alterations of participants suffering from xenomelia are the cause or the consequence of the longstanding desire for an amputation. It is well conceivable that years of adaptation of the brain to the desire for leg amputation, and the accompanying pretense to be an amputee (Giummarra et al., 2011; Hilti et al., 2013) could have caused the abnormalities found in the thalamus and basal ganglia. These issues remain pressing questions for future investigations using other study designs, more persons with xenomelia and wider populations with different signs of BIID.

4.3. Conclusions

Half a decade of neuroscientific research provides strong evidence that the unwanted limbs of persons with xenomelia might be misrepresented at different levels of the sensorimotor system. It has been shown that the cortical morphology is altered in xenomelia in the right SPL, IPL, S1, S2 and the anterior insula (Hilti et al., 2013) and that the subcortical structures putamen, caudate nucleus, pallidum and thalamus showed tissue displacements in subregions housing somatotopic representations. These regions contribute to the sensorimotor integration of single body parts, to the reconstruction of an "image" of the body as a whole and finally to the experience that one's self is anchored to this body. Up to now, subcortical structures received little attention in this context. The thalamus and the basal ganglia in particular process, transmit and integrate sensorimotor information and are involved in the preparation and execution of movements. The motor loop of the basal ganglia-thalamo-cortical circuit continuously subserves a somatotopic representation of all body parts. The findings reported here support the involvement of these subcortical structures in xenomelia, albeit with a pattern of laterality, which may be less clear than that previously described for the cortical architecture (Hilti et al., 2013).

In conclusion, we found structural alterations in the sensorimotor system of persons with xenomelia suggesting a misrepresentation of the legs in somatotopically organized sensorimotor regions of the thalamus and basal ganglia. Together with previous findings of corresponding cortical abnormalities, these results constitute a neural correlate for a disorder still neglected by medical health professionals at large, but being the source of tremendous suffering for those affected.

Conflict of interest

All authors declare that there are no competing interests.

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