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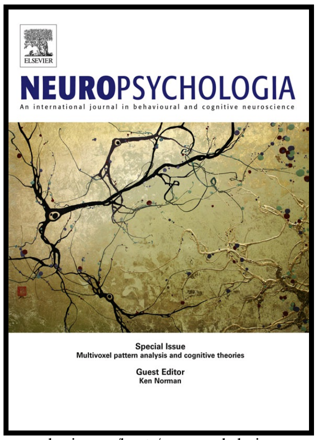

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Brain activity elicited by viewing pictures of the own virtually amputated body predicts xenomelia

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Abstract

Background: Xenomelia is a rare condition characterized by the persistent desire for the amputation of physically healthy limbs. Prior studies highlighted the importance of superior and inferior parietal lobuli (SPL/IPL) and other sensorimotor regions as key brain structures associated with xenomelia. We expected activity differences in these areas in response to pictures showing the desired body state, i.e. that of an amputee in xenomelia.

Methods: Functional magnetic resonance images were acquired in 12 xenomelia individuals and 11 controls while they viewed pictures of their own real and virtually amputated body. Pictures were rated on several dimensions. Multivariate statistics using machine learning was performed on imaging data.

Results: Brain activity when viewing pictures of one's own virtually amputated body predicted group membership accurately with a balanced accuracy of 82.58% (p=0.002), sensitivity of 83.33% (p=0.018), specificity of 81.82% (p=0.015) and an area under the ROC curve of 0.77. Among the highest predictive brain regions were bilateral SPL, IPL, and caudate nucleus, other limb representing areas, but also occipital regions. Pleasantness and attractiveness ratings were higher for amputated bodies in xenomelia.

Conclusions: Findings show that neuronal processing in response to pictures of one's own desired body state is different in xenomelia compared with controls and might represent a neuronal substrate of the xenomelia complaints that become behaviourally relevant, at least when rating the pleasantness and attractiveness of one's own body. Our findings converge with structural peculiarities reported in xenomelia and partially overlap in task and results with that of anorexia and transgender research.

Keywords

Amputation desire; Body integrity identity disorder; Classification; Caudate nucleus; Desired body state; fMRI; Inferior parietal lobule; Limb amputation; Machine learning; Prediction; Superior parietal lobule; Support vector machine; Xenomelia.

1. Introduction

Xenomelia (McGeoch, et al., 2011), also known as body integrity identity disorder (First, 2005; First & Fisher, 2012) or apotemnophilia (Brang, McGeoch, & Ramachandran, 2008), is an unusual and rare condition in which sufferers express the persistent desire for the amputation of limb(s) that are physically fully functioning. Xenomelia individuals typically report that their unwanted limb(s) do not belong to themselves and that they would feel better if the limb(s) were to be removed (Blanke, Morgenthaler, Brugger, & Overney, 2009). Psychiatric and neurocognitive assessments of xenomelia individuals reveal no known disease that could account for the amputation desire, and especially the absence of psychotic disorders has been repeatedly reported (Blom, Hennekam, & Denys, 2012; Brugger & Lenggenhager, 2014; First, 2005; Hilti, et al., 2013; van Dijk, et al., 2013).

Since it has been proposed that xenomelia might be a neurological disorder (Brang, et al., 2008; McGeoch, et al., 2011), particularly a new right parietal lobe syndrome (McGeoch, et al., 2011), there is growing evidence that both brain structure (Blom, et al., 2016; Hänggi, Bellwald, & Brugger, 2016; Hänggi, et al., 2017; Hilti, et al., 2013) and brain function (Hänggi, et al., 2017; McGeoch, et al., 2011; van Dijk, et al., 2013) differ between xenomelia individuals and controls as reviewed elsewhere (Brugger, Christen, Jellestad, & Hänggi, 2016). There is evidence that social components might play a role in the condition as well (Brugger, Lenggenhager, & Giummarra, 2013).

Structural and functional neuroimaging studies in xenomelia revealed that the right superior (SPL) and inferior parietal lobule (IPL) (Hänggi, et al., 2017; Hilti, et al., 2013; McGeoch, et al., 2011; van Dijk, et al., 2013), right anterior insula (Brang, et al., 2008; Hilti, et al., 2013), and right primary and secondary somatosensory cortex (SI and SII, respectively) (Hilti, et al., 2013; van Dijk, et al., 2013), particularly its left leg representation (Hänggi, et al., 2017; Hilti, et al., 2013) are altered in the condition compared with controls. The paracentral lobule, supplementary motor area, basal ganglia, thalamus, and the cerebellum (Blom, et al., 2016; Hänggi, et al., 2016; Hänggi, et al., 2017) are additionally altered in xenomelia.

Taken together, there is strong evidence that many areas of the sensorimotor system and the insula are altered in xenomelia individuals as revealed by anomalies in cortical thickness and surface area derived from surface-based morphometry (Hilti, et al., 2013). Differences in the magnetoencephalographic signal (McGeoch, et al., 2011) and neuronal activity measured with functional magnetic resonance imaging (fMRI) (van Dijk, et al., 2013) in response to tactile stimulation have been reported as well. Anomalies have also be found in structural and functional connectivity derived from diffusion tensor imaging-based fibre tractography and seed-to-seed-based correlation analyses of resting state fMRI data, respectively (Hänggi, et al., 2017), and in thalamic, putaminal, and pallidal shape (Hänggi, et al., 2016).

Intriguingly, all these brain regions are associated with the construction and the maintenance of a coherent body image (Berlucchi & Aglioti, 2010; Gerardin, et al., 2003; Giummarra, Gibson, Georgiou-Karistianis, & Bradshaw, 2008; Moseley, Gallace, & Spence, 2012; Tsakiris, Hesse, Boy, Haggard, & Fink, 2007; Wolbers, Weiller, & Buchel, 2003).

Investigations of healthy human subjects provide strong evidence that both SPL and IPL mediate body ownership (Kammers, et al., 2009) and are key for the integrative mental imagery of the configurations of limbs (Wolbers, et al., 2003). In particular the right-hemispheric SPL was involved in monitoring illusory limb displacements, independent of the limb’s laterality (Naito, et al., 2005). In addition, primary and secondary somatosensory hand representations are crucial in mediating the illusion of a rubber hand, where the visual observation of a rubber hand being touched simultaneously with the experience of touch to one's own hand evokes the sensation of an incorporation of the rubber hand (Tsakiris, et al., 2007) and leads to a diminished animation of the real hand (Moseley, et al., 2008). With respect to the homeostatic state of the body and interoceptive awareness, the insula predominately in the right hemisphere is key for establishing and maintaining the sense of body ownership (Craig, 2009, 2011; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Karnath & Baier, 2010; Moseley, et al., 2012).

Here, we investigated the neuronal response to different types of body-related pictures showing either one's own desired body state or one's own undesired body state. Similar paradigms as the one used here have already been applied to anorexia nervosa patients and transgender individuals (Feusner, et al., 2016; Fladung, et al., 2010). For that purpose, to our knowledge for the first time, individual stimuli comprising photos of one's own body (and a control body as well) in different positions were constructed and edited according to the individual amputation desire of the xenomelia subjects. We compared 12 xenomelia individuals with 11 male controls with respect to whole-brain functional activity when viewing these body-related pictures. Activity was measured with fMRI in response to six different categories of body-related pictures: the real own body / a control body, the own body virtually amputated / a control body virtually amputated, and the own body virtually amputated with prosthesis / control body virtually amputated with prosthesis. Subsequently to the fMRI session, these pictures were also rated with respect to pleasantness, intensity, attractiveness and sexual arousal.

We hypothesized that viewing the desired state of one's own body, i.e. that of an amputee in xenomelia and that of a non-amputated body in controls, evokes differential brain activity compared with brain activity when viewing one's own undesired body state, i.e. a non-amputated body in xenomelia and an amputated body in controls. Differential brain activity is expected to be present mainly in brain regions associated with the construction and maintenance of a coherent body image such as the parietal cortices (SPL and IPL), but also in brain regions housing limb representations such as the primary and secondary somatosensory cortex, basal ganglia, thalamus, premotor cortex, supplementary motor area as well as the insular cortex that is key for the homeostatic state of the body and interoceptive awareness. It has already been shown that all these brain regions are structurally and/or functionally conspicuous in xenomelia subjects as reviewed elsewhere (Brugger, et al., 2016).

In addition to the brain regions associated with body representations, we also expected differential brain activity in limbic regions associated with emotional processing due to the fact that viewing the desired or undesired body state also elicits differential affective states. With respect to the direction of effects and based on the small corpus of the functional neuroimaging literature in this condition, we expected increased as well as reduced activity in xenomelia compared with healthy male controls (Hänggi, et al., 2017; McGeoch, et al., 2011; van Dijk, et al., 2013).

2. Subjects, materials and methods

2.1 Subjects

Thirteen male individuals with xenomelia were recruited via Internet. One subject quit the fMRI session and withdrew from the study and was therefore excluded. The mean age of the remaining 12 individuals was 46.5 years (standard deviation (SD)=11.6 years, range 32-68 years) and eight of them achieved a university degree. Nine individuals whished an amputation of the left leg (at the height of the thigh), one of the right leg, and the remaining two of both legs. Seven individuals were heterosexuals and five homosexuals. For nine of the 12 individuals, the desire for limb amputation also has a sexually arousing component.

Additionally, twelve healthy male controls were recruited. One control subject produced strong motion-related artefacts during fMRI and was therefore excluded. Mean age of the remaining 11 controls was 41.9 years (SD=11.0 years, range 29-65 years) and eight of them achieved a university degree.

Inclusion criterion for xenomelia was the persistent desire for an amputation of one or both legs that has lasted since childhood (Brugger, et al., 2016; First & Fisher, 2012). Exclusion criteria were MRI incompatibility or any psychiatric or neurological disorder other than xenomelia. All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics review board.

2.2 Psychiatric and psychometric assessments

The Brief Symptom Inventory (BSI) (Franke, 2000), which is a short form of the Symptom-Checklist-90-Revised (SCL-90-R) (Franke, 2002) was applied. It assesses the psychological strain with respect to different symptoms and consists of 53 items. Nine scales measure somatization, compulsivity, uncertainty in social contacts, depression, anxiety, aggression and hostility, phobic fear, paranoid thinking, and psychoticism. The three main global indices are the Global Severity Index (GSI), Positive Symptom Distress Index (PSDI) and Positive Symptom Total (PST). For analysis, the raw values of each BSI scale were added and then transformed into T-values and percent ranks. Values between 40 and 60 are not conspicuous. Test duration is about 7-10 minutes. The BSI and the SCL-90-R were applied only to the individuals with xenomelia. Control subjects were assessed for psychiatric or neurological disorders by the psychologists/medical doctor in our team in the early recruitment phase. We enrolled a short clinical anamnesis that revealed no psychiatric or neurological disorder.

2.3 Post-scanning questionnaire for evaluation of the corporeal stimuli

After the MRI, the subjects were asked to answer four questions regarding each picture (see below) presented during the fMRI. The subjects were asked to estimate the following items on a seven-step Likert-type scale: (1) how pleasant/unpleasant the pictures were, (2) how emotionally intense the pictures were, (3) how appealing / attractive the subjects look on the pictures, and (4) how sexually arousing the pictures were. These ratings were conducted for pictures showing the own body as well as for those showing the control body. The question how appealing / attractive the control body looks on the pictures was not answered by most study participants due to an incorrect wording of this question. Hence, we do not report the attractiveness ratings for all three categories of the control stimulus.

2.4 Magnetic resonance imaging data acquisition

MRI scans were acquired on a 3.0 Tesla Siemens Allegra whole-body scanner (Siemens Healthcare, Erlangen, Germany) at the Brain Imaging Centre of Frankfurt on the Main, Germany. Further imaging parameters were as follows: repetition time (TR) = 2.5 s (mosaic acquisition TR = 65.7 ms per slice); echo time (TE) = 30 ms; field of view (FOV) = 192 x 192 mm^2; matrix 64 x 64 pixels; in-plane spatial resolution = 3 x 3 mm^2, slice thickness = 3 mm; number of slices = 38; flip angle α = 90°. Two runs were performed, each consisting of 291 brain volumes. A structural T1-weighted MRI scan was acquired in addition to using a magnetization-prepared rapid gradient echo (MP-RAGE) sequence with a measured and reconstructed spatial resolution of 1 x 1 x 1 mm^3. Further imaging parameters were as follows: TR = 2.3 s; inversion time (TI) = 2.3 s; TE = 3.93 ms; FOV = 256 x 256 mm^2; matrix 256 x 256 pixels; slice thickness = 1 mm; number of slices = 160; flip angle α = 12°.

2.5 Stimuli construction

The stimuli were especially constructed for the present study. Photos in different positions were taken of each xenomelia individual and control. These individual photos were then edited in Adobe Photoshop CS2 to produce three different categories of stimuli, i.e. of the own real body (Fig. 1A), own body virtually amputated as individually desired (Fig. 1B) and the own body virtually amputated with prosthesis (Fig. 1C). We included the pictures of the own body virtually amputated with prosthesis because most of the subjects suffering from xenomelia reported that they would prefer wearing a prosthesis when are in public, in contrast to not wearing a prosthesis when are at home or in private situations.

please insert Fig. 1 about here

The same three categories were constructed for a control body, i.e. a body of another male person. Therefore, each study participant viewed six different categories of stimuli: the own real body, the own body virtually amputated, the own body with prosthesis after virtual amputation, a real control body, a control body virtually amputated, and a control body with prosthesis after virtual amputation. The side and extent of the amputations was matched between groups. All participants viewed the same person in the control conditions. Each stimulus category contained 40 different pictures representing 40 different positions that were matched across subjects resulting in 240 pictures in total. The digital stimuli were scaled 312 x 350 (width x height) pixels and were presented during fMRI scanning with the help of the Presentation software (version 10.3, https://www.neurobs.com/).

2.6 Experimental procedures and task instructions

The task required passive viewing of the stimuli or the fixation cross (baseline) combined with attention control (see below). Subjects were instructed to attentively view the pictures and to give vent to their feelings if any emotional reactions emerged. The stimuli were randomly presented in a block design and the procedure can be divided into three parts. The first functional run with stimulus presentation lasted 12 minutes 17 seconds followed by a second run of stimulus presentation of the same time. In the third part, the structural T1-weighted image was acquired within 8 minutes and 37 seconds. 120 pictures were presented per run divided into 24 blocks. Each block contained 5 pictures and each picture was presented for 4 seconds resulting in a block length of 20 seconds. A stimulus category was divided into 8 blocks. After each block, a baseline condition of 10 seconds followed and the subject was instructed to focus on a black cross in front of a white background. The blocks were presented randomly and each stimulus was presented only once to avoid habituation effects.

To view the pictures sharply, the mirror was calibrated for each subject individually because the images were projected by a Sony Beamer (Type VPL-XP20, 1400 ANSI) onto a screen located cranially to the head of the subject. Attention was controlled for by instructing the subjects to react to appearing red rectangles by pressing a button held in their hand. The red rectangle was presented for 390 ms 36 times randomly distributed over the 48 blocks of both runs and balanced across the six picture categories. We did not detect any difference in this attentional control measure, i.e. both groups detected more than 95% of the red rectangles, suggesting that attention levels were comparable between groups.

2.7 Functional magnetic resonance imaging data processing

Functional MRI data were preprocessed and statistically analysed using statistical parametric mapping (SPM12) software tool (release 6470, www.fil.ion.ucl.ac.uk/spm/) running under MATLAB (version 2013b, http://www.mathworks.com/products/matlab/). The preprocessing of the functional MRI data was based on the batch file preproc_fmri.mat (with default values) that is part of the SPM12 distribution (folder batches) and consistent of the following steps: 1) slice timing correction, 2) realignment and unwarping, 3) segmentation of the T1-weighted image, 4) coregistration of the functional onto the structural image (estimate only), 5) linear and non-linear normalization of the T1-weighted MRI image, 6) smoothing of the functional data with a Gaussian kernel of full width at half maximum of 8 mm in each direction.

2.8 First level statistics

The preprocessed functional images were statistically analysed using the general linear model (GLM) approach implemented in SPM12. The first level statistics (fixed effects analysis) of the functional MRI were performed with the batch file stats1_within_subject_fmri.mat (folder batches of SPM12 distribution) with default values except for micro-time resolution and onset, which were set to 38 and 19, respectively. This accounted for the fact that slice time correction was applied. As recommended for SPM analyses, the baseline was not modelled explicitly in the statistical models.

2.9 Two different masks to extract the features

We expected differential brain activity in response to the corporeal stimuli between individuals with xenomelia and healthy male controls especially in the right SPL (Hilti, et al., 2013; McGeoch, et al., 2011). Since a few fMRI datasets did not have complete coverage of the whole brain (missing some superior and inferior slices), we constructed two different masks to extract the features. This was especially important because the most superior part of the SPL was not covered entirely in four subjects and this brain structure is a key region in xenomelia (Hilti, et al., 2013; McGeoch, et al., 2011; van Dijk, et al., 2013). Therefore, for the main findings reported in the present manuscript we used a mask that includes only the brain regions that have complete coverage in all 23 subjects, whereas for the additional results reported in the Supplementary Materials we used a whole brain mask that also included the regions that were not entirely covered in a few subjects. Nevertheless, both masks yielded comparable results.

2.10 Machine learning and support vector machine

For multivariate statistics, a binary support vector machine classifier (Lemm, Blankertz, Dickhaus, & Muller, 2011) adopted from the field of machine learning was applied. We used the Pattern Recognition for Neuroimaging data Toolbox (PRoNTo, http://www.mlnl.cs.ucl.ac.uk/pronto/) (Schrouff, et al., 2013) for both classifying groups and predicting the affect while subjects viewed stimuli. Briefly, given a dataset D={xi, yi}, i=1…N, consisting of pairs of samples (or feature vectors) $x_i \in R^d$ and labels y_i, the objective in supervised pattern recognition analysis is to learn a function from the data that can accurately predict the labels, i.e. $f(x_i)=y_i$, of unseen or new patterns (Lemm, et al., 2011; Schrouff, et al., 2013). If the labels are discrete values, the learned function $f(x_i)=y_i$ is denoted a classifier model and if the labels are continuous values the learned functions are called regression models. The data are commonly separated into disjoint datasets, i.e. a training set and a test set, and the analysis commonly proceeds in two phases (Pereira, Mitchell, & Botvinick, 2009; Schrouff, et al., 2013).

An algorithm learns some mapping between patterns and the labels on the training set during the training phase and during the test phase, the learned function is used to predict the labels from formerly unseen samples in the test set (Schrouff, et al., 2013). In the linear case, for example, the learned function depends on a linear combination of the feature vectors x_i, i.e. $f(x_i)=w_0+w^T x_i$. The weights $w \in R^d$ are the model parameters learned in the training phase and represent the relative contribution of each feature to the predictive task (Schrouff, et al., 2013).

For the binary classifications, we applied a binary support vector machine, and for predictions of the behavioural measures a kernel ridge regression. All models were performed as they are implemented in PRoNTo. We used a common n-fold leave-one-subject-out cross-validation scheme as implemented in PRoNTo for both the classifications and regressions. This means that we excluded one subject and trained the algorithm on the remaining n-1 subjects and then tested it on the excluded subject. This procedure was repeated for each subject resulting in 23 folds after which the resulting accuracy measures were averaged. In this way, independence of the training and testing sample was guaranteed. All learning models for the classifications used hyperparameter optimization for the parameter C in the range from 1 to 1,000 in steps of 100. The support vector machine parameter C accounts for the trade-off between the width of the support vector machine margin and the number of support vectors (Schrouff, et al., 2013). All learning models for the regressions used hyperparameter optimization for the parameter K in the range from 0.001 to 1 in steps of 10 using kernel ridge regression. The kernel ridge regression parameter K controls for the regularization (Schrouff, et al., 2013).

2.11 Statistical analyses

Instead of analysing the data with a classical GLM mass-univariate approach on the second-level, we applied multivariate statistics using a machine learning approach (Lemm, et al., 2011) for our main analyses. We classified each subject as being a xenomelia individual or a control solely based on the subject's brain activity while viewing the following six categories of stimuli: pictures of the real own / control body, virtually amputated own / control body, and virtually amputated own / control body with prosthesis. For reasons of completeness, a classical GLM mass-univariate approach on the second-level was additionally applied.

To extract brain features that will be fed into the support vector machine, we used the contrast files produced in the first-level statistics in SPM12, i.e. we contrasted the activity in each of the six conditions with that of the baseline. Binary classifications were used to predict group membership and regressions to predict different aspects of emotion and cognition experienced during viewing of the stimuli such as pleasantness, intensity, attractiveness, and sexual arousal of the pictures.

We report balanced accuracy, sensitivity, specificity and area under the receiver operating characteristic (ROC) curve for the classifications and correlation coefficient (r), explained variance (r^2) and mean squared error (MSE) for the regressions. The area under the ROC curve measures the classification accuracy (discrimination ability) of a test and it is defined as the percentage of randomly drawn pairs for which the test result is true. An area of 1.0 represents a perfect test, whereas an area of 0.5 represents a worthless test. Area values between 0.70-0.80, 0.80-0.90, and 0.90-1.00 are considered to represent a fair, good, and excellent test performance, respectively. To compare classification accuracies against chance level, we performed 1,000 permutations. To localize the brain regions with highest accuracy, weight maps were computed that sum up the voxel-wise weights within a region of interest (ROI). We used the automated anatomical labelling atlas (Tzourio-Mazoyer, et al., 2002) with 90 ROIs.

Age and the ratings of the pictures (see Table 2) were compared by performing nonparametric Mann-Whitney U-tests for between-group comparisons and Wilcoxon tests for within-group own-control pictures comparisons using IBM SPSS Statistics (version 24 for Mac OS X). Psychiatric and psychological measures were compared with normative values using t-score transformation. If not otherwise stated, two-tailed p-values are reported at a significance level of $p < 0.05$. For the psychiatric and psychological measures, we additionally report q-values that were corrected for multiple comparisons using the false discovery rate (FDR) correction procedure, whereas for the ratings of the pictures we report FDR-adjusted p-values only due to the large number of tests performed on these ratings.

3. Results

3.1 Demographic, psychiatric and psychological measures

There were no significant differences between groups with respect to age (Mann-Whitney-U-test, z=-1.17, p=0.26). The distributions of their educational levels (8 subjects with a university degree in each group) and handedness (all right handers) were comparable between groups. Psychiatric and psychological measures were assessed in xenomelia individuals only and compared with normative population values (Franke, 2000, 2002) (Table 1).

Table 1. Results of the psychiatric and psychological measures

Reference test value is T = 50	N	Mean	SD	T-value	DF	p-value	FDR q-value
BSI global indices							
GSI	11	56.91	11.18	1.95	10	0.079	0.189
PSDI	11	55.91	9.64	1.94	10	0.081	0.162
PST	11	57.36	11.72	1.99	10	0.075	0.225
BSI subscales							
Somatization	11	55.55	11.72	1.50	10	0.165	0.247
Compulsivity	11	50.09	7.75	0.04	10	0.971	0.971

Uncertainty in social contacts	11	51.91	11.46	0.53	10	0.610	0.732
Depression	11	58.55	11.89	2.27	10	0.046*	0.276
Anxiety	11	55.18	10.05	1.63	10	0.134	0.229
Aggression / hostility	11	55.55	6.12	2.86	10	0.017*	0.204
Phobic fear	11	48.82	6.94	-0.54	10	0.602	0.802
Paranoid thinking	11	50.91	10.62	0.27	10	0.792	0.864
Psychoticism	11	57.45	10.47	2.25	10	0.048*	0.192

Note that data from one individual are missing and therefore mean and standard deviation are based on eleven subjects only. Reference test value is mean T=50 and SD=10. T-values were computed according ((mean sample–mean population)/(SD/√DF)). Note that raw values below 40 or above 60 are considered aberrant, whereas values between 40-60 are considered normal (Franke, 2000, 2002). * Statistical significance disappears after false discovery rate (FDR) correction for multiple comparisons (q-value). Abbreviations: BSI, brief symptom inventory; DF, degrees of freedom; GSI, global severity index; PSDI, positive symptom distress index; PST, positive symptom total; SD, standard deviation.

There were no significant deviations from normative values in most of these variables, except for depression, aggression/hostility and psychoticism, which were slightly elevated in xenomelia individuals. However, statistical significance disappears after correction for multiple comparisons.

3.2 Post-scanning questionnaire for evaluation of the corporeal stimuli

Mean ratings of the stimuli shown during the fMRI task are presented in Table 2. The six categories of different corporeal pictures were rated with respect to pleasantness, intensity, attractiveness, and sexual arousal. Each stimulus category contained 40 different pictures so that each study participant performed 240 ratings in total. As mentioned above, we excluded the attractiveness ratings of the control body in the present results.

Many statistical comparisons are possible (Table 2), but we were mainly interested in the ratings of the own body rather than in that of the control body. Furthermore, the data were measured with an ordinal scale and therefore complex models are not possible when using the more appropriate nonparametric statistical tests. Therefore, we made a compromise and used parametric statistics, i.e. mixed analysis of variance (mANOVA), to get a first overview of which factor is significant. Subsequently, we used nonparametric statistics for the post hoc between-group comparisons of the ratings using the Mann-Whitney U-test and within-group own vs. control and amputated vs. non-amputated pictures comparisons using the Wilcoxon test.

Table 2. Ratings of the post-scanning questionnaire for evaluation of the corporeal stimuli.

Pictures / Questions	Pleasantness		Intensity		Attractiveness		Sexual arousal	
	Xenomelia	Control	Xenomelia	Control	Xenomelia	Control	Xenomelia	Control
	Mean (SD) p-values	Mean (SD) p-values	Mean (SD) p-values	Mean (SD) p-values	Mean (SD) p-values	Mean (SD) p-values	Mean (SD) p-values	Mean (SD) p-values
Own real body as it is	4.02 (1.15) 0.056/0.11	4.97 (1.28) 0.038	3.08 (1.38) 0.69/0.035	2.84 (1.70) 0.068	3.26 (1.27) 0.54/n.a.	3.75 (1.45) n.a.	1.43 (0.61) 0.62/0.18	1.17 (0.47) 0.068
Own body virtually amputated	6.23 (0.60) <0.001/0.009	1.84 (0.59) 0.16	5.92 (0.86) 0.098/0.011	4.67 (1.75) 0.014	5.95 (0.93) <0.001/n.a.	1.45 (0.41) n.a.	3.54 (1.88) 0.002/0.017	1.00 (0.00) 1.00
Own body virtually amputated with prosthesis	5.70 (0.70) <0.001/0.017	2.11 (0.87) 0.068	5.26 (0.99) 0.17/0.017	4.20 (1.80) 0.006	4.99 (0.93) <0.001/n.a.	1.76 (0.89) n.a.	2.97 (1.67) <0.001/0.038	1.00 (0.01) 0.22
Control real body as it is	3.85 (0.63) 0.21	4.11 (1.18)	2.13 (1.05) 0.86	2.68 (1.71)	Not reported	Not reported	1.26 (0.65) 0.54	1.04 (0.10)
Control body virtually amputated	4.79 (0.89) <0.001	2.38 (1.04)	3.73 (1.56) 0.48	3.30 (1.67)	Not reported	Not reported	2.02 (1.47) 0.068	1.00 (0.00)
Control body virtually amputated with prosthesis	4.71 (1.12) 0.002	2.60 (0.88)	3.96 (1.52) 0.34	3.14 (1.72)	Not reported	Not reported	1.84 (1.48) 0.93	1.00 (0.00)

Note: Means and standard deviations are shown. Higher values represent higher pleasantness, intensity, attractiveness, and sexual arousal of the stimuli. P-values were computed using nonparametric the Mann-Whitney U-test for between-group comparisons and the Wilcoxon test for own vs. control pictures comparisons within groups. The first p-value reported in the xenomelia column represents that of the between-group comparison (xenomelia vs. control), whereas the second p-value in the xenomelia column indicates that of the own-control pictures comparison for the xenomelia individuals. The p-value reported in the control column represents that of the own-control comparison for the control subjects. The question how appealing the control subject looks on the pictures had suboptimal wording and was therefore not answered by a majority of study participants. Hence, we do not report the attractiveness ratings for all three categories of the control stimulus. The p-values of the comparisons between the real and the amputated versions of the own body within groups are reported in the text only (pages 17 and 18). The p-values reported are adjusted for multiple comparisons using the false discovery rate (FDR) correction procedure and statistically significant FDR adjusted p-values are printed in bold. Abbreviations: n.a., not assessed; n.s., not significant; SD, standard deviation.

First, we ran a 2x3 mANOVA for each scale separately using GROUP (two levels: xenomelia / control) as between-subject factor and PICTURE (six levels: real own / control body as it is, own / control body virtually amputated and the own / control body virtually amputated with prosthesis) as within-subject factor. The mANOVA of pleasantness revealed no significant main effect of the factor PICTURE ($F_{(2,21)}$=2.18, p=0.14, η_p^2=0.18), but showed a significant and strong interaction between the factors PICTURE and GROUP ($F_{(2,21)}$=33.22, p=4.4E-7, η_p^2=0.77). The mANOVA of intensity revealed a significant main effect of PICTURE ($F_{(2,21)}$=10.70, p=0.001, η_p^2=0.52), but showed no significant interaction between PICTURE and GROUP ($F_{(2,21)}$=0.70, p=0.51, η_p^2=0.07). The mANOVA of attractiveness revealed no significant main effect of PICTURE ($F_{(2,21)}$=1.51, p=0.25, η_p^2=0.13), but showed a significant and strong interaction between PICTURE and GROUP ($F_{(2,21)}$=29.43, p=1.1E-6, η_p^2=0.75). The mANOVA of sexual arousal revealed a significant main effect of PICTURE ($F_{(2,21)}$=6.79, p=0.006, η_p^2=0.41) and also showed a significant interaction between PICTURE and GROUP ($F_{(2,21)}$=9.15, p=0.002, η_p^2=0.48).

In summary, except for the intensity scale, the ratings on all other scales showed strong interactions between the factors PICTURE and GROUP. This suggests that pleasantness, attractiveness as well as sexual arousal of these pictures are rated differently depending on whether the pictures showing the desired body state of a group, i.e. the own body as it is, which is the desired state of the control subjects, or the own body (virtually) amputated and (virtually) amputated with prosthesis, which is the desired body state of the xenomelia individuals.

As predicted, xenomelia individuals rated the pictures of the own body virtually amputated and virtually amputated with prosthesis more pleasant (p = 0.009 and p = 0.011, respectively), more attractive (p = 0.011 and p = 0.009, respectively) and even more sexually arousing (p = 0.017 and p = 0.017, respectively) than own real body pictures, whereas, except for sexual arousal (p = 0.098 and p = 0.098, respectively), the converse was true for the controls (pleasantness: $p = 0.013$ and $p = 0.013$, respectively; attractiveness: $p = 0.014$ and $p = 0.026$, respectively).

Pictures showing the own real body were rated less pleasant by xenomelia individuals compared with controls ($p = 0.056$, corrected for multiple comparisons), whereas intensity ($p = 0.69$), attractiveness ($p = 0.54$) and sexual arousal ($p = 0.62$) ratings of these pictures did not differ between groups. The pictures showing the own body virtually amputated or virtually amputated with prosthesis were rated more pleasant ($p < 0.001$ and $p < 0.001$, respectively), not more intensive ($p = 0.098$ and $p = 0.17$, respectively), more attractive ($p < 0.001$ and $p < 0.001$, respectively) and even more sexually arousing ($p = 0.002$ and $p < 0.001$, respectively) by the xenomelia individuals compared with controls. Even the control body amputated elicited strong ratings in xenomelia subjects. The statistics regarding the ratings of the own and control body pictures can be found in Supplementary 1.1.

We did not perform direct statistical comparisons between the pictures showing the virtually amputated body and the pictures showing the virtually amputated with prosthesis because we did not expect large differences between the two conditions. However, xenomelia subjects tented to rate the own pictures without the prosthesis more pleasant, more intense, more attractive, and even more sexually arousing compared with those showing the prosthesis.

3.3 Classification of group membership

Xenomelia individuals can quite accurately be classified solely based on brain activity evoked when viewing pictures of the own virtually amputated body in contrast to baseline. Brain activity when viewing these pictures predicted group membership with a balanced prediction accuracy of 82.58% ($p=0.002$), sensitivity of 83.33% ($p=0.018$), specificity of 81.82% ($p=0.015$) and an area under the ROC curve of 0.77. In other words, of the 12 xenomelia individuals two and of the 11 control subjects also two were misclassified.

The pictures presenting the own virtually amputated body with prosthesis predicted group membership less accurately compared with the pictures presenting the own virtually amputated body without prosthesis, but still with a balanced accuracy of 65.15% (p=0.092), sensitivity of 66.67% (p=0.22), specificity of 63.64% (p=0.14) and an area under the ROC curve of 0.76, although these accuracy measures did not reach statistical significance.

The pictures of the other four categories of stimuli, i.e. the real own body (balanced accuracy = 47.35%, p=0.23; sensitivity = 58.33%, p=0.40; specificity = 36.36%, p=0.23; area under ROC curve = 0.37), virtually amputated control body (balanced accuracy = 43.18%, p=0.58; sensitivity = 50.00%, p=0.60; specificity = 36.36%, p=0.66; area under ROC curve = 0.56), virtually amputated control body with prosthesis (balanced accuracy = 60.98%, p=0.14; sensitivity = 58.33%, p=0.42; specificity = 63.64%, p=0.14; area under ROC curve = 0.54), and a real control body (balanced accuracy = 56.44%, p=0.24; sensitivity = 58.33%, p=0.40; specificity = 54.55%, p=0.30; area under ROC curve = 0.52), did not elicit brain activity that can predict group membership above chance level.

To show that pictures of one condition significantly better classifies than pictures of another condition we applied McNemar’s test for paired nominal data. The accuracy of the classification based on the pictures showing the own body virtually amputated was not significantly better than the accuracy based on the pictures showing the own body virtually amputated with prosthesis (the pictures showing the own body virtually amputated classified significantly better than that of the own real body ((The pictures showing the own body virtually amputated discriminate significantly better than the pictures showing the control body virtually amputated with prosthesis (the pictures showing the own body virtually amputated with prosthesis did not classify significantly better than that of the control body amputated with prosthesis (In summary, the pictures showing the own body virtually amputated classified significantly better than all other conditions except that of the own body virtually amputated with prosthesis, whereas the pictures showing the own body virtually amputated with prosthesis did not classify significantly better than all other conditions.

The right SPL and bilateral IPL are among the regions with the highest predictive power for the pictures showing the own virtually amputated body (Table 3). In addition, both amygdalae are also among the 15 brain regions with the highest prediction accuracy.

Table 3. Brain regions showing highest classification accuracy when applying a binary support vector machine on the pictures showing the own virtually amputated body.

Rank	Region of interest (ROI)	ROI weight (%)	ROI size (voxel)	Exp. ranking	MNI space COG coordinates (x / y / z)		
1	Temporal_Pole_Mid_L	2.75	12	1.43	-37	15	-34
2	Temporal_Pole_Sup_L	2.63	640	3.52	-41	15	-20
3	Parietal_Sup_R	2.45	504	2.78	25	-59	62
4	Parietal_Inf_R	2.33	1,046	3.52	45	-46	50
5	Occipital_Sup_L	2.13	835	5.17	-18	-84	28
6	Parietal_Sup_L	2.07	418	5.17	-24	-60	59
7	Occipital_Sup_R	1.87	953	7.35	23	-81	31
8	Cuneus_L	1.76	1,176	9.74	-7	-80	27
9	Cuneus_R	1.76	1,136	8.78	13	-79	28
10	Temporal_Pole_Sup_R	1.68	402	11.30	57	-22	7
11	Rectus_R	1.64	243	13.17	7	36	-18
12	Amygdala_L	1.64	187	14.00	-24	-1	-17
13	Occipital_Inf_L	1.57	519	13.30	-37	-78	-8
14	Occipital_Mid_R	1.53	1,219	14.17	36	-80	19
15	Amygdala_R	1.43	205	17.91	26	1	-18

Regions predicted a priori are in bold. Abbreviations: COG, centre of gravity; Exp. ranking, expected ranking across cross-validation folds; Inf, inferior; L, left; Mid, middle; MNI; Montreal neurological institute; R, right; Sup, superior.

The right SPL is the region with the highest predictive power and the right IPL that with the second highest predictive power (Table 4) regarding the pictures of the own virtually amputated body with prosthesis. In addition, the left SPL, right angular gyrus, left caudate nucleus and the left supplementary motor area are also among the 15 brain regions with the highest predictive power. The right supplementary motor area is on rank 18.

Table 4. Brain regions showing highest classification accuracy when applying a binary support vector machine on the pictures showing the own virtually amputated body with prosthesis.

Rank	Region of interest (ROI)	ROI weight (%)	ROI size (voxel)	Exp. ranking	MNI space COG coordinates (x / y / z)		
1	Parietal_Sup_R	4.12	504	1.17	25	-59	62
2	Parietal_Inf_R	3.24	1,046	2.61	45	-46	50
3	Temporal_Pole_Mid_L	3.12	12	2.30	-37	15	-34
4	Occipital_Sup_L	2.46	835	4.09	-18	-84	28
5	Occipital_Sup_R	2.11	953	5.70	23	-81	31
6	Parietal_Sup_L	2.08	418	6.17	-24	-60	59
7	Temporal_Pole_Mid_R	1.94	37	10.26	56	-37	-1
8	Angular_R	1.93	1,366	7.39	45	-60	39
9	Cuneus_L	1.89	1,176	8.52	-7	-80	27
10	Frontal_Mid_Orb_R	1.75	197	11.65	32	53	-11
11	ParaHippocampal_R	1.74	538	10.09	24	-15	-20
12	Occipital_Inf_L	1.59	519	12.13	-37	-78	-8
13	Cuneus_R	1.58	1,136	12.57	13	-79	28
14	Caudate_L	1.58	962	12.74	-12	11	9
15	Supp_Motor_Area_L	1.53	1,618	13.22	-6	5	61

Regions predicted a priori are in bold. Abbreviations: COG, centre of gravity; Exp. ranking, expected ranking across cross-validation folds; Inf, inferior; L, left; Mid, middle; Orb, orbital; MNI; Montreal neurological institute; R, right; Sup, superior; Supp, supplementary.

Since we used multivariate statistics, the direction of the effects cannot be explicitly indicated because both voxels with increased as well as those with reduced brain activity can be part of the same ROI. However, when we performed a post-hoc mass-univariate directed random effect analysis in SPM, the right SPL seems to be rather hyperactive than hypoactive in xenomelia compared with controls. Yet this finding must be interpreted with caution because these directed mass-univariate t-tests did not reach statistical significance when corrected for multiple comparisons.

The same classifications as reported above for the restricted mask can be found for the whole brain mask in Supplementary Material 2.2. Both masks delivered comparable classification accuracies and the most predictive sensorimotor regions are visualised in Fig. 2. Here we present only the nine sensorimotor brain regions that have been predicted a priori, i.e. brain regions that have already been reported to be structurally and/or functionally altered in xenomelia. Some of these regions are listed in all Tables (3, 4, S1 and S2), whereas other regions are listed only in one of these Tables.

please insert Fig. 2 about here

With respect to the 15 brain regions with the highest classification accuracy, it is intriguing that almost all brain regions are either the predicted sensorimotor regions or visual areas such as the inferior, middle and superior occipital gyrus, cuneus and calcarine cortex (Table 3 and 4 and Supplementary Table 1 and 2). In contrast to the sensorimotor and visual areas that were found consistently on comparable ranks across tasks (amputated and amputated with prosthesis) and across masks (restricted and whole-brain), the temporal pole finding should not be interpreted at all due to its small size as well as its dependence on the mask used to extract the features.

3.4 Direction of activation differences

To provide information about the direction of the activity differences, i.e. whether the pictures presented elicited increased or decreased brain activity in one group compared to the other, we extracted the mean activity of the nine ROIs shown in Fig. 2 to descriptively show the activity differences between groups while viewing pictures of the own body virtually amputated. To account for the fact that the classifier (support vector machine) used is multivariate in nature, i.e. considering voxels with increased or decreased activity between groups simultaneously, we report these activity differences between groups separately for activations and deactivations relative to the baseline.

please insert Fig. 3 about here

It is obvious from Fig. 3 that participants with xenomelia showed mainly either stronger activation (Fig. 3, left panel) or weaker deactivation (Fig. 3 right panel) compared with healthy controls.

3.5 Whole-brain mass-univariate analyses

For reasons of completeness, we also conducted mass-univariate statistical analyses across the whole brain for all six contrasts of interest. These analyses, however, revealed only one small cluster in the left lower superior parietal lobule (MNI coordinates x / y / z: -20 / -34 / 78, 19 voxels in size, family-wise corrected cluster p = 0.004) with increased activity in xenomelia subjects when viewing pictures of the own body virtually amputated with prosthesis. All other contrasts did not reveal any significant activation difference between groups.

3.6 Prediction of pleasantness, intensity, attractiveness, and sexual arousal of the corporeal stimuli within each group separately

We also tried to predict, within each group separately, the ratings of pleasantness, intensity, attractiveness, and sexual arousal of the different categories of corporeal stimuli that were viewed during fMRI and rated subsequently.

We neither found significant predictions of the ratings of the pictures showing the own body virtually amputated nor virtually amputated with prosthesis. The prediction accuracies of the pleasantness, intensity, attractiveness, and sexual arousal ratings across both groups are reported in Supplementary 1.3.

4. Discussion

The present study provides first evidence for a dissociation in functional brain activations between xenomelia subjects and controls in response to individual pictures representing their desired or undesired body states. In particular, the pictures of the desired amputated body of xenomelia individuals elicited differential neuronal activations capable of classifying these sufferers from healthy control subjects based solely on neuronal activations. This divergent pattern of brain activation might represent a neuronal substrate of the complaints reported by subjects with xenomelia. “This limb is mine, but I do not want it” is an often heard complaint associated with xenomelia (Berti, 2013). Other illustrative first-hand descriptions of such complaints can be found elsewhere (Brugger, et al., 2016).

4.1 General considerations

It is important to note that our imaging findings show only a single dissociation because only the condition where xenomelia subjects viewed their desired body state (amputated) and the male controls viewed their undesired body state (amputated) classified subjects significantly above chance level. We were unable to accurately classify the subjects based on brain activity when xenomelia subjects viewed their undesired body state (real body as it is) and the male controls viewed their desired body state (real body as it is). This may suggest that xenomelia subjects viewed their own real body more or less normally, but showed differential brain activity from controls only when viewing their desired body state, i.e. the state of an amputee. The absence of a double dissociation might provide space for alternative explanations (see limitations below).

Although we were unable to predict the ratings (maybe due to low statistical power) of the pictures shown during fMRI scanning based solely on brain activity when viewing these pictures, most of these ratings are significantly different between groups and / or between own and control body pictures within groups (Table 2). This might suggest, albeit indirectly, that the differential brain activations observed in xenomelia subjects during fMRI scanning become relevant on the behavioural level by modulating the pleasantness and attractiveness ratings of the pictures presented.

To our knowledge for the first time, our results demonstrate that xenomelia individuals can accurately be classified solely on brain activity elicited by viewing their desired body state, i.e. that of an amputee. The brain regions with the highest predictive values, contributing most to the accurate classifications, are exactly those associated with the construction and maintenance of a coherent body image such as the (right) SPL and IPL, paracentral lobule and caudate nucleus (Berlucchi & Aglioti, 2010; Gerardin, et al., 2003; Giummarra, et al., 2008; Moseley, et al., 2012; Tsakiris, et al., 2007; Wolbers, et al., 2003). Beside these body-related brain regions, visual areas in the occipital lobe also contributed considerably to the accurate classifications (see below).

The prominent role of the right SPL and IPL in the classifications fits well with the findings of the few existing neuroimaging studies on xenomelia. The right SPL is a key area that has been repeatedly shown to be functionally and structurally altered in xenomelia individuals compared with controls (Hänggi, et al., 2017; Hilti, et al., 2013; McGeoch, et al., 2011; van Dijk, et al., 2013).

Along with classifying groups accurately based on brain activity while viewing the picture with different body states, the subjects can also be grouped based on the pleasantness, attractiveness and sexual arousal ratings of the corporeal pictures as assessed immediately after fMRI. The ratings of the desired body states of both groups, i.e. the rating of the pictures showing the own body amputated in xenomelia with those showing the real body in controls, were directly compared. All these ratings are significantly higher in xenomelia individuals compared with controls. This pattern of ratings might be rooted in the fact that for xenomelia individuals, the desired state is a virtual, not yet achieved state and thus is experienced more pleasant, intense, attractive and even more sexually arousing compared with controls. In contrast, for the controls the desired body state is already achieved (their real body) and thus these subjects rated their body state less pleasant, intense, attractive and not sexually arousing at all compared with xenomelia individuals.

In summary, xenomelia individuals rate the pictures of their desired body state (that of an amputee) more pleasant, intensive, attractive and sexually arousing than pictures of the undesired body state (real body), whereas controls rate the picture of their desired body state (real body) more pleasant, intensive, and attractive, but not sexually arousing than pictures of the undesired body state (that of an amputee). This double dissociation nicely underscores that the two groups do prefer quite different body states. A recently published study revealed that there is also an implicit preference for incomplete bodies in xenomelia (Macauda, Bekrater-Bodmann, Brugger, & Lenggenhager, 2017). The phenomenon that the amputation desire, the imagination of an amputee or looking at an amputee is associated with sexual arousal in most xenomelia subjects is not new (Blom, et al., 2012; Brugger, et al., 2016) and is also reflected in the ratings provided by the xenomelia individuals investigated here.

The intensity ratings of the pictures, irrespective of the type of stimuli, do not differ between groups. This might be rooted in the simple fact that both groups rated the same type of pictures as similar intense independent of the fact that a picture represents the desired or undesired body state. The missing difference in intensity ratings is also reflected in the predictions of the intensity ratings based on the brain activity maps, which all failed.

As expected, the limbic system was involved in the classifications, although only marginally compared with the sensorimotor system. Among the brain regions that showed highest classification accuracy when applying a binary support vector machine on the pictures showing the own virtually amputated body, the left and right amygdala were the limbic structures among the 15 brain regions contributing most to this classification and are on rank 12 and 15, respectively (Table 3). The right parahippocampal gyrus was also involved in the classification based on brain activity elicited by viewing pictures of the own virtually amputated body with prosthesis (Table 4). Together with dopaminergic involvement (i.e. caudate in the prosthesis condition), differential amygdalar and parahippocampal activity between groups might underline the high emotional component of the desired amputated body in xenomelia individuals, although it has been shown that general emotional processing is unaffected in individuals with xenomelia (Bottini, Brugger, & Sedda, 2015).

Parts of the temporal pole showed high classification accuracies and are adjacently located to the amygdala. However, the temporal pole is not part of the limbic system and the evidence for its involvement in emotional information processing is rather slim as revealed by a post-hoc meta-analytic search in the database Neurosynth (http://www.neurosynth.org/) with the search term “emotional” or “affective”. The involvement of the temporal pole in the classifications must be interpreted with caution. The left and right middle temporal pole ROI are very small (12 and 37 voxels, respectively). Indeed, when comparing the restricted with the whole-brain mask classifications, it becomes obvious that in contrast to the parietal and occipital regions, which showed high accuracy with both masks, the middle temporal pole regions do not classify any longer between groups when using the whole-brain mask for feature extraction. However, one should be careful in declaring our temporal pole finding as an imaging artefact because a recently published study applied magnetoencephalography to measure brain activity in response to somatosensory stimulation of the breast, a body part that feels incongruent to most presurgical female-to-male-identified transgender individuals, and the hand, a body part that feels congruent. That study reported reduced activation in the supramarginal gyrus and secondary somatosensory cortex, but increased activation in the temporal pole for chest sensation in female-to-male transgender compared to non-transgender females (Case, Brang, Landazuri, Viswanathan, & Ramachandran, 2017; Feusner, et al., 2016; Manzouri, Kosidou, & Savic, 2017). Whether the temporal pole might be important for body-related representations and its associated disorders in general remains to be established in future studies.

Finally, it is worth mentioning that the supplementary motor area is differentially activated between groups in the prosthesis condition. It might be that the strong desire to be an amputee and the daily imaginations of being an amputee with prosthesis as well as the routine of many xenomelia individuals to pretend to be an amputee (i.e. by tying up a leg and using crutches) lead to a neural representation of a body with prosthesis in the supplementary motor area.

Such a speculation might be supported by recent findings showing that brain activity in the missing-hand area of congenital one-handers is compensation-specific, i.e. brain activity even occurs when legs or lips were used in a compensatory fashion to accomplish tasks normally performed with both hands such as to open a bottle (Hahamy, et al., 2017).

4.2. Visual areas also showed differential brain activity

Besides the sensorimotor brain regions that are differentially activated in response to different corporeal-related stimuli in xenomelia compared with control subjects, lower and higher visual areas also showed distinct activation patterns between groups. Due to the fact that our a priori predicted brain regions based mainly on structural and on functional imaging findings using tactile stimulation tasks, we did not predict any involvement of visual areas a priori. However, it is very interesting that the differential activation of visual areas in xenomelia in response to pictures of corporeal-related stimuli is restricted to pictures showing their own desired body state, i.e. that of an amputee, but did not occur when xenomelia subjects are faced with pictures presenting either their unwanted body state (not amputated) or an amputated control body. Whether these activity differences in visual areas exclusively for pictures showing the own desired body state are directly related to xenomelia or could also be explained by other factors such as attention or familiarity remains to be investigated in future studies (see also limitations below).

4.3 Comparison with other mental disorders involving the own body

Although our specific task is a new paradigm when focusing on the content of the pictures and has neither been applied to other subjects nor been validated yet, similar tasks as the one used here have been applied in other patient groups as well. This shows that our task is not uncommon in research on disorders related to the body. The sensorimotor brain regions, and especially the parietal lobuli, found to be predictive in classifying xenomelia subjects from healthy male controls in the present study also revealed differential brain activity in anorectic patients when using tasks that are similar to our task (Friederich, et al., 2010; Miyake, et al., 2010; Sachdev, Mondraty, Wen, & Gulliford, 2008; Uher, et al., 2005) as well as in gender dysphoria individuals (Case, et al., 2017; Manzouri, et al., 2017). There was not only an overlap in the regions of the sensorimotor system, in particular the parietal cortices, between xenomelia and anorexia when presenting body-related stimuli, but also in visual areas. For instance, Feusner and colleagues applied fMRI and used pictures that have been morphed between the sex assigned at birth and the sex congruent with the gender identity in female-to-male gender dysphoria individuals and reported weaker connectivity within visual networks in female-to-male gender dysphoria individuals compared to heterosexual female controls (Feusner, et al., 2016). Sachdev and colleagues used fMRI while subjects viewed images of self and non-self (matched for body mass index) and reported the complete absence of occipital activations in anorectic subjects, but only when viewing pictures of the self and not when viewing pictures of the non-self, whereas healthy control subjects showed occipital activations in both conditions (Sachdev, et al., 2008).

4.4 Clinical considerations

First and with respect to the clinical relevance of our findings, it is important to note that we neither need fMRI nor machine learning to diagnose xenomelia because individuals suffering from the condition explicitly claim the desire for healthy limb amputation. From a clinician's point of view, we still need to better understand the clinical features and the deep reasons that characterize xenomelia to better understand the syndrome per se. Whether using visual stimuli and fMRI to distinguish individuals with xenomelia from normal controls may even be of potential clinical utility remains to be determined. Second, considering psychiatric symptoms, there are elevated scores in xenomelia compared with the population norm values with respect to the depression, aggression/hostility and psychoticism scale. However, the significant deviations disappear when correcting for multiple testing and therefore these elevated psychiatric scores should not be interpreted, or only with great caution. Furthermore, other empirical xenomelia studies using different samples also did not report any psychiatric peculiarities in subjects suffering from xenomelia (Blom, et al., 2012; Blom, et al., 2016; Brugger, et al., 2016; First, 2005; Hilti, et al., 2013; van Dijk, et al., 2013), except for depressive symptoms that are the consequence of the life-long struggle with the "foreign limb" and the associated amputation desire.

With respect to nosology, there are attempts to rename the condition body integrity identity disorder (super category of xenomelia) as body (integrity) dysphoria, quite in historical parallel to the terminological fate of gender identity disorder, now labelled gender dysphoria (Beek, Cohen-Kettenis, & Kreukels, 2016). If the dysphoric aspects were to outweigh the aspects of the amputation desire, one would expect to observe that pictures of the real (own) body lead to brain activations that should classify group membership more accurately than pictures showing the own virtually amputated body. However, the fact that classification accuracies for xenomelia persons were high and statistically significant only for pictures of the own virtually amputated body (contrasted to baseline) but not for pictures of the own normal body (contrasted to baseline) might suggest that xenomelia participants weigh the amputation desire stronger than the dysphoria associated with the unwanted "foreign limb". Hence, one could argue that it might be questionable whether body dysphoria is the most adequate term to describe this condition.

4.5 Methodological considerations

The classifications and regressions reported in the present study were all based on whole-brain analyses and not on a priori selected cortical and subcortical regions of interests. Only to gain information about which brain regions are most discriminative, i.e. for the extraction of the weights, which indicate how strong a particular region contributes to the classifications and regressions, we used an ROI approach (AAL90 atlas) that averaged the voxel-wise weights obtained from the whole-brain voxel-wise analyses within each region for better visualisation and interpretation.

Due to incomplete coverage of the whole brain, i.e. missing some superior and inferior slices in some participants, we constructed two different masks to extract the features. However, the results reported were comparable between the two different types of masks (compare Tables 3 and 4 with Supplementary Tables 1 and 2, respectively, and especially the involvement of the right SPL, the key region in xenomelia (Hilti, et al., 2013; McGeoch, et al., 2011; van Dijk, et al., 2013), was not affected by the fact that its most superior part was not fully covered during fMRI scanning in two xenomelia individuals and two male controls.

4.6 Limitations

The present study has some limitations. First, the sample size (n = 23) is small. However, considering the rarity of the condition, the sample size is, in our opinion, acceptable. We did not run a power analysis in advance to determine the number of participants due to the a priori known restricted availability of xenomelia patients. Second, a recent review highlighted the great potential of neuroimaging data for single subject prediction of various disorders, but also revealed that the main bottleneck of this machine learning approach in neuroimaging is still the limited sample sizes (Arbabshirani, Plis, Sui, & Calhoun, 2017). Although their Fig. 3C suggests an inverse correlation between accuracy and sample size, this has been interpreted with caution due to the heterogeneity of the studies, i.e. these studies not only differ in sample size, but also in many other factors such as the type of experimental task, classifier, feature selection procedure and the cross-validation scheme. However, focussing on the disorder schizophrenia and the modality fMRI (the same modality as used in the present study) (see their Table 3), it is obvious that accuracy can be comparable between studies that differ in sample size (compare the study by Costafreda and colleagues with that by Bleich-Cohen and colleagues) (Bleich-Cohen, et al., 2014; Costafreda, et al., 2011) or that studies with larger sample sizes reported higher accuracy than those using smaller samples (compare the two studies by Castro and colleagues) (Castro, Gomez-Verdejo, Martinez-Ramon, Kiehl, & Calhoun, 2014; Castro, Martínez-Ramón, Pearlson, Sui, & Calhoun, 2011). In the present study, however, we used a linear support vector machine that is less prone to overfitting and we found classification accuracies that are comparable with those reported in this recent review (Arbabshirani, et al., 2017). For example, a task fMRI study (confrontation naming task) in healthy elderly (n = 24) with either low (n = 11) or high risk (n = 13) for developing Alzheimer's disease using different classifiers as used in the present study found an overall classification accuracy of 83.3% (Andersen, Rayens, Liu, & Smith, 2012) that is comparable with the accuracies achieved in the present study. Nevertheless, future multicentre studies in xenomelia and data sharing initiatives of already sampled data might help increase the number of study participants considerably. Third, because of the small sample size it was not possible to build subgroups to investigate differences with respect to lateralisation of the amputation desire, i.e. whether the left leg or the right leg or even both legs are the target limb(s) of amputation. Fourth, the absence of a double dissociation with respect to the imaging data (in contrast to the behavioural data) provides space for alternative explanations. One might argue that differential brain activity only occurs if the pictures show a not yet accomplished body state (the amputated state) in contrast to pictures showing the already accomplished body state (the real body as it is). However, if true, then one has to expect a similar effect when subjects view these categories of pictures of the control body. We did not observe such an effect. Last, the sexual orientation of the male controls was been assessed so we cannot exclude that neural activity might also be influenced by the sexual orientation. This shortcoming might especially be relevant for the post fMRI ratings of attractiveness and sexual arousal of the stimuli that exclusively consisted of male bodies. However, brain activity classifies only for pictures showing the own body virtually amputated, but did not classify for pictures showing a control body amputated rendering sexual orientation as an explanation of the effects observed less likely.

4.7 Conclusion

To conclude, our study furnish evidence that xenomelia is represented in the brain by different neuronal patterns. We showed for the first time that xenomelia can be predicted objectively by differential neuronal activity in response to pictures showing the desired body state mainly in brain regions associated with the construction and maintenance of a coherent body image as well as in areas associated with visual processing. This further supports structural neuroimaging findings that individuals with xenomelia have at least different, if not even distorted, neural representations of the own body or parts of it and might suggest that the complaints reported by xenomelia subjects are real. The findings of the present study also highlight the need to help xenomelia patients by accepting their amputation desire as a medical condition (Brugger, et al., 2016) and by providing therapeutic interventions such as a body-related therapy, psychotherapy or even elective limb amputation (Noll & Kasten, 2014). How the findings of the present study can be used to develop new therapeutic approaches in xenomelia remains to be explored. Potential therapeutic interventions might include virtual reality technology capable of implementing a virtual life with the desired body state, i.e. to be an amputee or transcranial magnetic or direct current stimulation applied to body-related brain regions such as the right SPL and IPL that showed highest classification accuracy in the present study.

Conflict of interest

All authors declare that there are no competing interests.

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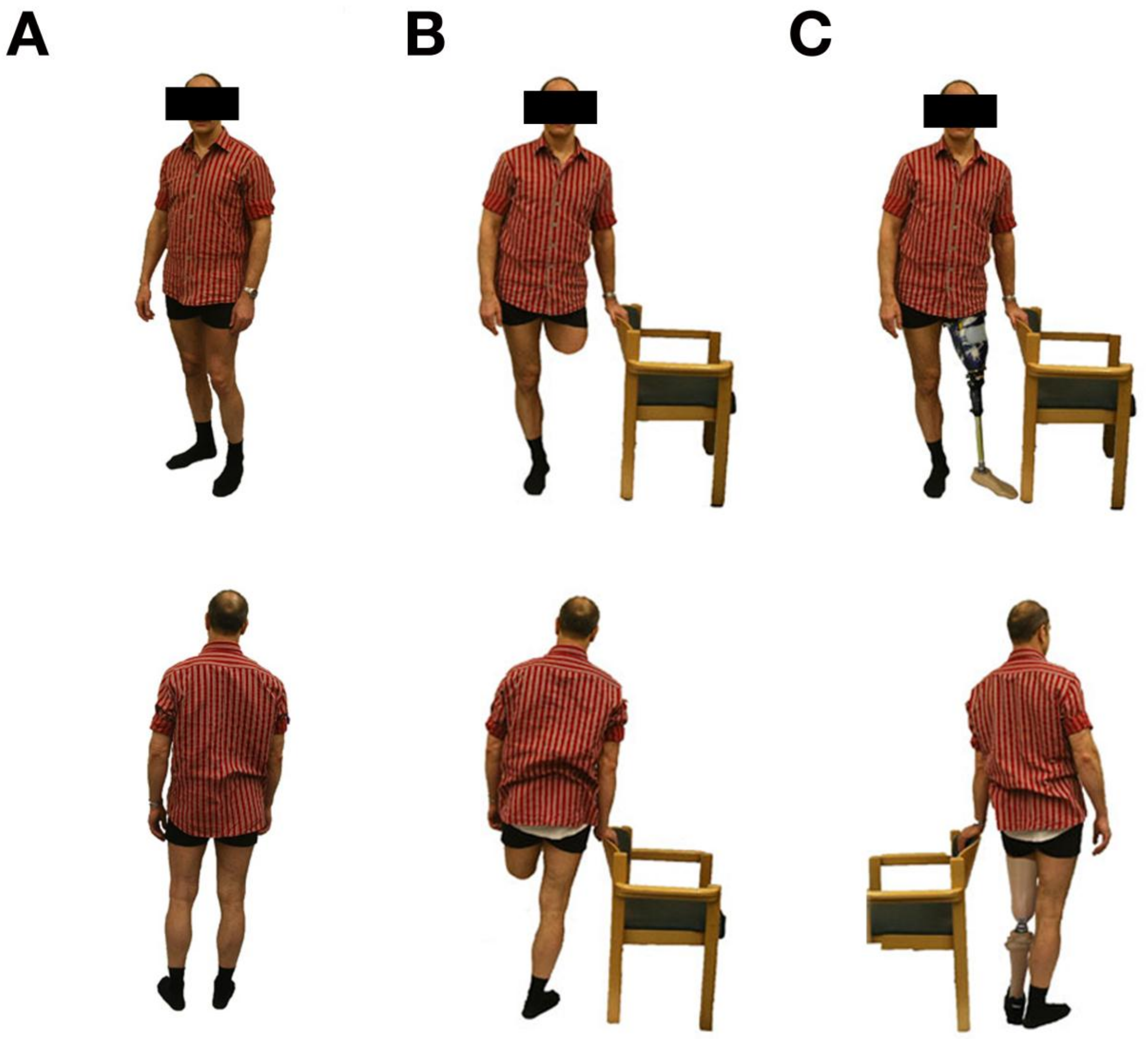
Figure legends

Figure 1. Examples of stimuli used in the present study. A) The own real body as it is. B) The own body virtually amputated as desired by the xenomelia individual. C) The own body with prosthesis after the desired virtual amputation. The photos presented are from a healthy control subject. Note that there are also photographs with prosthesis where no non-body parts (chair, table, crunches) were visible and it deceives from the perspectives shown in 1B and 1C that legs of the chair are missing. Only in 1C bottom panel, two legs of the chair were cut away. Photographs are printed with an explicit written permission by the control subject shown.

Figure 2. Sensorimotor brain regions with high classification accuracy. Bilateral superior parietal lobule (red), bilateral caudate nucleus (blue), right inferior parietal lobule (blue), right postcentral gyrus (yellow), right angular gyrus (green), left paracentral lobule (cooper), and left supplementary motor area (green). x, y, and z represent Montreal neurological institute space coordinates. There is a right-hemispheric preponderance of parietal regions in the classifications.

Figure 3. Direction of effects within brain regions with high classification accuracies. Shown are activation (left panel) and deactivation (right panel) differences between groups within the sensorimotor regions with high classification accuracies presented in Fig. 2 while viewing pictures of the own body virtually amputated. To account for the fact that the classifier used is multivariate in nature, i.e. considering voxels with increased or decreased activity simultaneously, we report these activity differences between groups separately for activations and deactivations relative to the baseline. Data are presented only descriptively and we did not compute any p-value to avoid biased results due to double-dipping. Bars represent the mean plus/minus 95% confidence interval. Abbreviations: ANG, angular gyrus; Caud, caudate nucleus; IPL, inferior parietal lobule; L, left; PCL, paracentral lobule; PoCG, postcentral gyrus; R, right; SMA, supplementary motor area; SPL, superior parietal lobule.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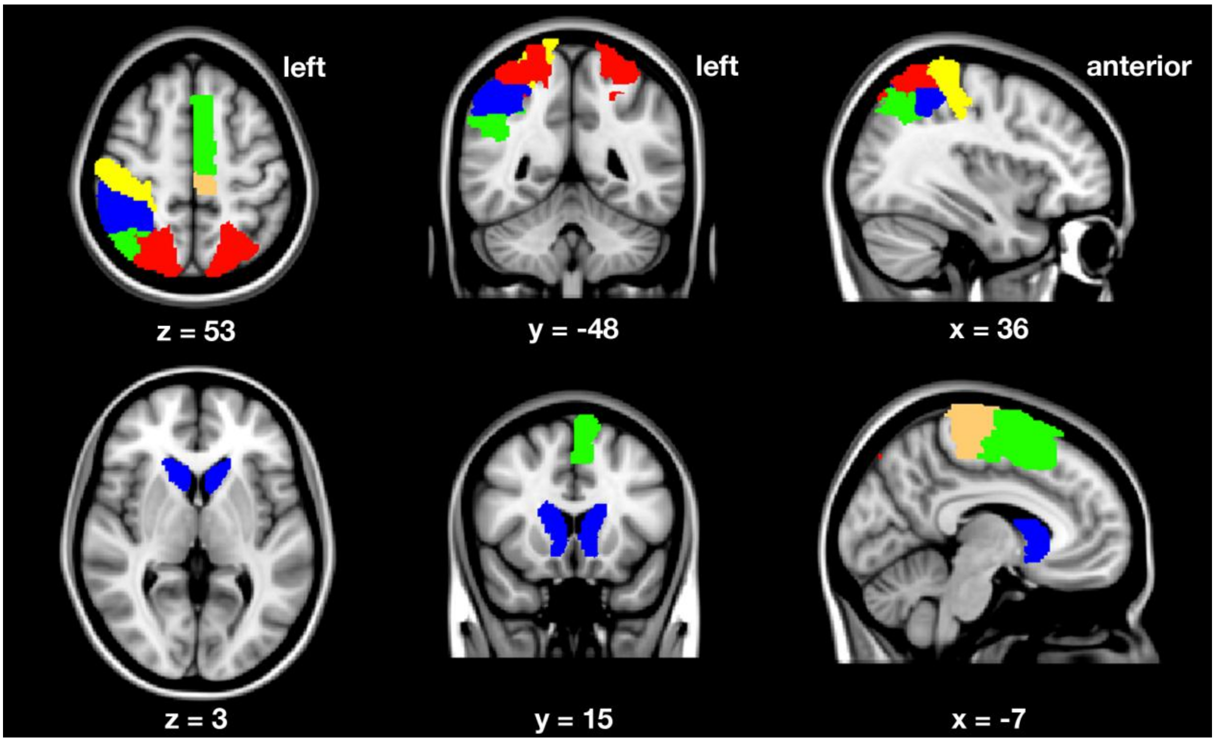
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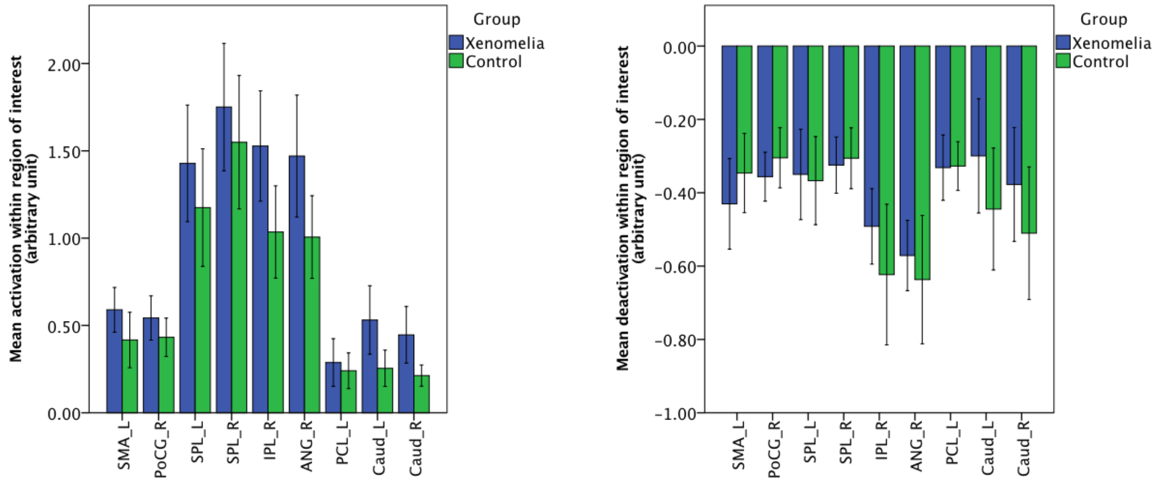

Highlights

- Confronting xenomelia subjects with pictures showing their desired body state
- Pleasantness/attractiveness ratings are higher for amputated bodies in xenomelia
- Brain activity predicts xenomelia when viewing pictures of one's own amputated body
- Pictures of one's own amputated body with prosthesis classifies xenomelia subjects
- Activity in parietal and visual areas showed highest classification accuracy